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NEUROLOGY: PAST, PRESENT, AND FUTURE*

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What is neurology? The subtitle of the journal *Brain* is "A Journal of Neurology," and the scope of that journal may therefore be taken as a useful index of the scope of neurology. Any volume of *Brain* contains articles on the physiology, anatomy, and biochemistry of the nervous system, on neuropathology, on the psychological and psychiatric aspects of nervous disorders, and on clinical neurology, including neurosurgery. In the most comprehensive sense, then, neurology comprises all aspects of the normal and abnormal functioning of the nervous system. In one important respect neurology differs from all other branches of physiology and of medicine: it is concerned with that part of the human organism which is most distinctively human, and it is therefore unique among all branches of medicine in the extent of its contributions to scientific knowledge beyond the scope of animal physiology, through its study of the neural basis of all the psychological and physiological functions of man.

The Century of Nosography

Before the nineteenth century, though many isolated neurological observations had been made from the earliest times, neurology as a science can hardly be said to have existed. The nineteenth century was pre-eminently a century of nosography—of the recognition of syndromes and diseases. It would take far too long to enumerate all those which the nineteenth-century clinicians and pathologists delineated in neurology; instead I will trace the development of thought about two which still present us with unsolved problems.

Disseminated Sclerosis

Disseminated sclerosis was first recognized as a pathological entity by Cruveilhier (1835) and by Carswell (1838). Cruveilhier noted also the association of the pathological lesions with paraplegia in one case. Limited clinical and pathological studies were made by German authors, but it was Charcot and his school who first presented a coherent clinical picture. Indeed, to read Charcot's (1877) lectures on disseminated sclerosis is to realize how comparatively little has been added to our clinical knowledge of the disease since his day. Though Charcot maintained that "the multiplication of nuclei and the concomitant hyperplasia of the reticulated fibres of the neuroglia constitute the initial, fundamental fact, and necessary antecedent," and that "the degenerative atrophy of the nerve elements is consecutive and secondary," the breakdown of the myelin had not escaped his notice, for he drew attention to bodies containing fatty droplets—"granular bodies" exactly resembling "those which result from the disintegration of the medullary matter (myeline) in cases of nerve-section."

And then a century was to pass before our knowledge of the disease made a new and at present very tentative advance. Post-vaccinal encephalomyelitis was certainly not a new disease when an outbreak in the early 1920s attracted attention (Bastiaanse, 1925), and pathological studies of this and allied disorders following measles, and other exanthems, revealed acute inflammatory lesions of the nervous system both resembling and differing from disseminated sclerosis (Turnbull and McIntosh, 1926). This led experimental pathologists to study the production of acute demyelinating lesions in animals by the injection of brain tissue, a condition already recognized in man as a result of antirabic inoculation. Meanwhile other observations had suggested that some forms of demyelination, or failure of myelination, might be related to defects in the oligodendroglia, which stimulated research into the role of the glia in relation to the production of myelin. The present position of this research is well summarized in Lumsden's (1957) two chapters in "Modern Trends in Neurology" (second series) entitled "Some Aspects of the Chemistry of the Myelin and Sheath Cell Complex" and "Cell Structure and Cell Physiology in Relation to Myelin." Here we learn how biochemistry, tissue culture, the electron microscope, and electrophysiology are contributing to the fundamental knowledge of the nerve cell which we must possess if we are to understand the aetiology of disseminated sclerosis.

Parkinsonism

Now turn to another common nervous disease which exhibits a growth of knowledge parallel in time with that of disseminated sclerosis, but in some interesting respects different. In 1817 James Parkinson published his classical *Essay on the Shaking Palsy*. For a long time, however, this disease was confused with disseminated sclerosis, the differentiation being made in the mid-century by Charcot, amongst others, in the lectures from which I have already quoted. It was not until this century, however, that any light was thrown upon its pathology, chiefly owing to the discovery by Kinnier Wilson (1912) of the association between degeneration of the corpus striatum and symptoms resembling Parkinsonism. Lewy (1914) drew attention to the presence of cell degeneration in the putamen and globus pallidus and, later, in the substantia nigra. Almost exactly a century after Parkinson's publication epidemic encephalitis produced a new variety of Parkinsonism, and the relationship between the syndrome and lesions of the substantia nigra was confirmed. By this time it was

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recognized that Parkinsonism was merely a syndrome, resulting from a number of causes—cerebral atheroma, neurosyphilis, manganese and carbon monoxide poisoning amongst others—in addition to those already mentioned.

The association between the liver disease and the lenticular degeneration in Wilson's disease remained a puzzle until, quite recently, it was discovered that the fundamental disorder was an abnormality of copper metabolism, which is now being extensively studied. But why do the cells of the substantia nigra undergo degeneration in the spontaneous variety called paralysis agitans by Marshall Hall? In paralysis agitans we recognize one of the "presenile degenerations," a group which includes some of the most insidious and relentless nervous disorders, the presenile dementias, the progressive cerebellar degenerations, and motor neurone disease. Unless a lucky chance discloses unsuspected metabolic disturbances in patients suffering from these diseases, it is likely that we shall have to wait for more detailed knowledge of the metabolism of the nerve-cell before we can understand them.

While during the nineteenth century clinicians and pathologists, joined later by the bacteriologists, were establishing clinical syndromes and correlating them with their pathology and aetiology, during the second half of the century there was an increasing analysis of symptoms themselves, and the development of broad concepts of the functions of the nervous system. Examples of this are the discovery of the excitability of the brain by Fritsch and Hitzig (1870) and by Ferrier (1873), Jackson's observations on epilepsy and his ideas of the organization of function in the nervous system, Gowers's acute clinical observations, the large literature on aphasia, the concepts of localization and representation in the nervous system which emerged from all this work; and, just at the very end of the century, Babinski's (1896) account of his observations on the plantar reflex.

Contribution of the Twentieth Century

The contribution of the twentieth century to neurology has been so rich and varied that I can depict only the broad outlines. Fundamental to all subsequent work was the publication by Sherrington of *The Integrative Action of the Nervous System* in 1906. Sherrington's study of the reflex arc, the interaction between reflexes, inhibition and excitation, the synapse, a term which he had invented some years before, proprioceptors, decerebrate rigidity, and the physiological position and dominance of the brain opened for neurology a new world, the exploration of which, as we shall see, is still far from exhausted.

Between the beginning of the century and the first world war Head and Sir Gordon Holmes were advancing our knowledge of the neurology of sensation. Head's work on the peripheral nerves (Rivers and Head, 1908), though much of it has not stood the test of time, stimulated subsequent investigators, and I am sure he would have felt much interest in the recent ideas of the relation between quality of sensation and pattern of impulses in the peripheral nerves. We owe to this period also the work of Head and Thompson (1906) on sensation in the spinal cord, and Head and Holmes (1911) on the thalamic syndrome and sensory disturbances at the cortical level, and Sir Francis Walshe's (1914) application of Sherrington's ideas to the interpretation of the reflexes in paralysis of the lower limbs in man. The spinal injuries of the first world war stimulated still further the study of the reactions of the damaged spinal cord and bore fruit in the work of Head and Riddoch (1917), Riddoch (1917), and Walshe (1919). Gunshot wounds of the brain gave Holmes, who had already contributed to our knowledge of the cerebellar degenerations, the opportunity for his masterly studies of the disordered physiology of the cerebellum in man (Holmes, 1917, 1922) and the cortical representation of vision, and the higher visual functions (Holmes, 1918a, 1918b; Holmes and Lister, 1916).

Neurosurgery

Meanwhile neurosurgery was growing up. In its modern form it begins with the pioneer work of Horsley, who laid the foundations of neurosurgery not only as a technique but also as a sphere of applied physiology, in which he was followed by Cushing and Foerster, amongst many others. Neurosurgery brought in its train advances in neuroradiology—especially ventriculography and pneumo-encephalography, which we owe to Dandy, and cerebral angiography, the invention of Moniz—which may be said to have introduced a new dimension into neurology. In the treatment of the gliomas neurosurgery has proved disappointing, and we must look to a greater understanding of both tumour formation and the biochemistry of neuroglia for an effective answer to this distressing disease.

The contribution of neurosurgery to neurological knowledge arises chiefly out of the increased accuracy of location of cerebral lesions which it, with its ancillary investigations, has made possible, and hence the differentiation of disorders previously merged in a general picture of increased intracranial pressure. Though Cushing and Bailey (1928) and others had drawn attention to the vascular malformations of the brain before angiography was introduced, it is only since then that we have been able to estimate the frequency of these lesions and to recognize their varied symptomatology. Our knowledge of intracranial aneurysms has followed a somewhat similar course. It is surprising that what was presumably a common lesion went so long unrecognized. But it was not until the work of Fearnsides (1916) and Turnbull (1918) on their pathological aspects and, above all, Symonds's (1924–5) clinical and pathological contribution that we began to recognize subarachnoid haemorrhage. Even so, it was not until angiography became available that diagnosis could be in many cases accurate enough to raise the question of surgical treatment, the indications for which are still a matter of discussion. And it is largely to angiography that we owe the recognition of the symptomatology of atheroma of the internal carotid artery.

Electroencephalography

Electroencephalography was developing *pari passu* with these radiological techniques. Beginning with the discovery of Berger (1929) and Adrian and Matthews's (1934) pioneer applications of the method to neurophysiology, it was soon taken up in the clinical sphere by Gibbs, Gibbs, and Lennox (1937), Grey Walter (1938), and others. A quarter of a century's experience shows that in many patients suspected of an organic cerebral lesion or dysrhythmic disturbance it will add little to what can be learned by careful history-taking and clinical examination. Its chief diagnostic value lies in: (1) locating a lesion not otherwise localizable, or the confirmation of a localization otherwise in doubt; examples of this are the recognition and localization of a metastatic abscess or neoplasm in the brain, the presence of which might otherwise be unsuspected; (2) the demonstration of a dysrhythmia which confirms the suspicion of epilepsy made on clinical grounds; (3) the locating of an epileptogenic focus; and (4) the demonstration of diffuse degenerative or inflammatory processes, and even in some cases the detection of a type of dysrhythmia characteristic of the disease. It follows that, like all diagnostic aids, electroencephalography is of value only when the clinician knows what question to put to the machine, and how to interpret the answer it gives.

The uses of electroencephalography which I have enumerated have contributed greatly to the clarification of our understanding of epilepsy during the last twenty years. The idea that epilepsy should be regarded primarily as a symptom

is a very old one, expressed by Hughlings Jackson and stressed by Kinnier Wilson in his emphasis on "the epilepsies." For a long time, however, it seemed to be in conflict with the concept of idiopathic epilepsy. The effect of electroencephalography aided by neuroradiology has been greatly to extend our recognition of symptomatic or focal epilepsy by demonstrating foci of dysrhythmia or angiomas or areas of cerebral atrophy which elude clinical investigation. So it has proved possible more often to correlate the clinical features of an epileptic attack with an anatomical lesion; and here neurosurgery has contributed by making the cerebral cortex of the conscious epileptic patient available for electrical stimulation. Much, however, remains to be learned about the spread of focal epilepsy, the origin of generalized major epilepsy and petit mal, and the underlying basis of hereditary predisposition. The tendency to neural discharge must possess a biochemical basis, as the value of anticonvulsant drugs shows. The abnormal biochemical state may often be the result of a local structural lesion, but is it always so? The answer to this question may depend upon the neurophysiologists, who are now able to stimulate localized areas deep in the brain and study the resulting disturbances of cortical rhythm, which is but one application of electroencephalography to neurophysiology, about which I have more to say later.

Recent Developments in Neurophysiology

This brings me naturally to recent developments in neurophysiology. Encephalitis lethargica, epidemic in the years following 1916, showed a predilection for the basal structures of the cerebral hemispheres, the corpus striatum, the hypothalamus, and the upper part of the brain system. Some patients, particularly children and adolescents, exhibited striking physiological and psychological aberrations which attracted much attention, including obesity and genital atrophy, polydipsia and polyuria, and impulsive, aggressive, and irresponsible behaviour. During the following decade physiologists were producing similar abnormalities in animals by means of lesions at the base of the brain.

Diabetes insipidus, obesity, and gonadal atrophy were all attributed to localized lesions of the hypothalamus by Bailey and Bremer (1921), Camus and Roussy (1922a, 1922b), Smith (1927), and others, and this initiated a vast amount of work devoted to the study of the mutual relationships of the hypothalamus and the pituitary. Bard (1929) produced what he called "sham rage" in the cat by a lesion between the frontal lobes and the anterior part of the hypothalamus, and showed that this behaviour could be abolished by a section posterior to the hypothalamus. At about the same time the production of sleep-like states in animals by lesions deep in the central part of the brain stem provided an interpretation of the sleep disturbances of encephalitis lethargica. This work, thirty years ago, marks the beginning of three important developments in neurology: the correlation between behaviour disturbances and focal lesions of the brain; the study of the influence of the nervous system upon the endocrine system and so on the biochemistry of behaviour; and, lastly, the investigation of the central nervous regulation of the state of consciousness.

Now let us jump thirty years and see where these studies stand to-day. There have been numerous investigations of behaviour disturbances in animals produced in various ways, either by the ablation of comparatively large areas, such as the temporal lobe of Klüver and Bucy (1939), or by the destruction of more localized areas of cortex. By means of deeply implanted electrodes it has been possible to study the effects of stimulating localized deep structures. The application of electroencephalography to physiology has introduced a functional method of tracing the connexions of areas of the nervous system by making it possible to detect the remote responses to a stimulus. This is one of the methods which have been used to elucidate the relationship of the central reticular formation of the brain stem to consciousness, the effect of the activity of that region being correlated with the electrical state of the cerebral cortex and the behaviour of the animal.

The relationship between the hypothalamus and the endocrine system has been illuminated by such work as Verney's (1957) on the hypothalamic regulation of the renal excretion of water, and that of Harris and others, who have shown that individual nuclei of the diencephalon may act as chemoreceptors to particular hormones. Adrenaline, for example, acts upon the central reticular formation; and Harris, Michael, and Scott (1957) have shown that the implantation of very small amounts of stilboestrol into the hypothalamus of ovariectomized cats, but not elsewhere, results in full sexual behaviour in the absence of or with minimal development of the vaginal epithelium and uterus. Thus the central site of action of ovarian hormones in producing active sexual behaviour would seem to be in some part of the posterior hypothalamus or upper mid-brain.

Fifty years ago Sherrington was writing about excitation and inhibition, and the synapse. To-day the newest neurophysiological techniques are concentrated upon precisely these topics. Eccles (1957) has shown that it is possible to penetrate into the interior of the single nerve cell and analyse the transactions which are taking place across its membrane. Thus he has been able to differentiate the functions of the dendrites and the axon hillock and to show that discharge depends on depolarization and inhibition on hyperpolarization, stimulation and inhibition summing in their effect on the cell, as Sherrington foresaw. Hodgkin, Huxley, and Keynes have also studied the physicochemical behaviour of the neurone. Thus we are beginning to learn about the role of chemical transmitters at the synapse in the central nervous system, and the chemical basis of excitation and inhibition. Similar studies are showing what goes on at the myoneural junction.

Clinical Neurology To-day

Where does clinical neurology stand to-day? People sometimes speak as though nosography in neurology was almost exhausted, but this is quite untrue. The discovery of new diseases or syndromes, and equally the elaboration of the clinical pictures of existing ones, are partly a matter of seeing differences in what has hitherto been thought to be homogeneous. I have already shown how new diagnostic methods have contributed to this process in the case of epilepsy, cerebral angioma, intracranial aneurysm, and internal carotid atheroma. Radiography also played an important part in the recognition of the neurological manifestations of cervical spondylosis. Compression of the median nerve in the carpal tunnel is an example of a syndrome which seems to have become much commoner since its recognition shortly after the war. New diseases and the increased incidence of old diseases, together with changes in the age distribution of the population, have also altered the clinical landscape of neurology, producing, for example, the carcinomatous neuromyopathies and new infections such as acute inclusion encephalitis and benign myalgic encephalomyelitis, the "Royal Free disease." The neurological aspects of hypertension and atheroma are of growing importance. Involvement of the nervous system and muscles in collagen diseases is a new field now being explored, and, among the metabolic disorders, porphyria. Electromyography is throwing new light upon disorders of the lower motor neurone, the myoneural junction, and the muscles.

It might have been thought that after a century of study the main disorders of cerebral function would have been elucidated. Yet since the beginning of the war considerable additions have been made to our knowledge of the functions of the frontal lobe, the symptomatology of lesions of the temporal lobe and of the minor hemisphere, the agnosias and disorders of the body image, and the central regulation of consciousness. But the greater our knowledge of the effects of lesions of different parts of the

brain, the more apparent becomes our need for a clarification of our thought on the meaning of localization and representation in the nervous system. Such considerations are not to be regarded as merely the preoccupation of a few neurological schoolmen: they are fundamental to our understanding of how the nervous system works, and hence to the interpretation not only of symptoms but also of the observations of the neurophysiologist.

The Contribution of Neurology to Psychiatry

Hughlings Jackson (1932), writing of insanity, said in 1881: "We require a rational generalization so wide as to show on the physical side relations of diseases of the mind, which are for physicians nothing but diseases of the highest centres, to all other diseases of the nervous system. We have to find some fundamental principle under which things so superficially different as the diseases empirically named hemiplegia, aphasia, acute mania, chorea, melancholia, permanent dementia, coma, etc., can be methodically classified." If nearly eighty years later we ask how far Hughlings Jackson's requirement has been or is likely to be fulfilled, we should discover what is the essential neurological contribution to psychiatry, and what are its limitations.

Both neurologists and psychiatrists recognize in practice the validity of four kinds of aetiological factor in their work. (1) There are the causes which produce disorders of function by acting physically upon the nervous system. This wide field ranges from pathophysiology, which requires normal physiology for its interpretation, through neurochemistry to the visible changes studied by the neuropathologist. It is essentially the study of the nervous system as a physical object, behaving in health and disease according to the laws of the physics and chemistry of its constituent parts. (2) There is the study of the effects of the bodily changes of the kind which I have just described upon the mind. (3) We may approach the mind–brain relationship from the other side and observe the effects of mental changes upon the body, where we enter the field of what is commonly called psychosomatic medicine. (4) Finally, we may limit our study of causation to the psychological sphere, by interpreting psychological disorders in psychological terms—that is, asking how the patient's present mental state has been caused by his previous mental states. This aspect of psychiatry comprises psychopathology and psychotherapy in its various forms.

Although I began with physical and ended with psychological aetiology, this does not mean that I regard any one form as more fundamental or valuable than the rest. I might equally well have arranged them in the reverse order, with the same qualification. Nor does the fact that we must recognize these four varieties of aetiology in "neuropsychiatry" absolve us from the duty of applying the most rigid criteria of validity to the arguments which may be used at any aetiological level. Thus, the recognition that symptoms may be explained as psychogenic does not imply the acceptance of one particular theory of psychopathology or technique of psychotherapy. And the practitioner who gives due weight to the factors in all these aetiological fields is unlikely to accept too readily a psychological explanation for severe mental illness, merely because at the moment we are unable to explain it on physical grounds. And, since this classification is pragmatic, one form of causation does not exclude another. It is in the sphere of the first two categories of causation, which deal with neuropathology and with the influence of physical changes in the nervous system upon the mind, that we may expect to find the main contribution of neurology to psychiatry. I need not discuss long-familiar disorders like the dementias and mental defect, nor the psychological importance of the ever-increasing knowledge of the aphasias, agnosias, and disorders of the body image.

The actual or potential contributions of neurology to psychiatry could be illustrated from examples of the progress of neurology, some of which I have already given—the numerous symptoms of disturbances of the temporal lobe which may lead to disorders of awareness of the self and the external world, and may produce distortions of memory or states of fear, sorrow, disgust, loneliness, or depression (Williams, 1956). Whitty and Lewin's (1957) observations on cingulectomy throw an interesting light on the sense of reality. Sleep, dreams, illusions, and hallucinations are all subjects as appropriately studied by the neurologist as by the psychiatrist. Electric convulsion therapy and leucotomy act neurologically.

Thus the simple concept that the mind is dependent upon the brain has during recent years been increasingly refined and defined till now we know much, though still far too little, about the part played by the different areas of the brain in the regulation of consciousness, memory, emotional mood, and the integration of the personality.

If we compare the psychological disorders which can be explained in terms of psychological causation with those which we have reason to think are the result of physical changes in the nervous system, we note certain points of difference between them. The first relates to their neural basis. We know extremely little about the organization of memory in the brain, but it is surely clear that the nervous organization underlying one memory can differ from that underlying another only in respect of subtle differences in the arrangement of the finest nervous impulses, or perhaps synaptic resistances, over wide areas of the brain. It must follow, therefore, that no physical method which can be applied to the brain, whether surgical, electrical, or pharmacological, is capable of dealing with an individual past experience as such.

Interpretation of Mental Disorder

To put the matter in another way, when the mind is disordered as a result of disorder of the nervous system the neurological disorder is describable, actually or at any rate potentially, in physical terms, that is to say, in terms of the biochemistry of nerve cells or the gross structural changes familiar to the neuropathologist. When, however, the mind is disordered as a result of the reactions of the individual to his previous experiences, no such explanation in terms of biochemistry or morbid anatomy is possible. No doubt the neurological explanation is that certain nervous impulses are taking one pathway rather than another, *but the pathways themselves can be distinguished as healthy or unhealthy only in terms of the psychological states with which they are associated.* Here we reach the limitation of Hughlings Jackson's hopes for the neurological interpretation of mental disorder. Hemiplegia, delirium, and coma are states of body or mind which can be attributed to *physical* disorders of the nervous system, and it may well be that mania and melancholia, as Jackson suggested, and possibly ultimately schizophrenia, will be similarly explained. If so, the causes of these disorders could be described in purely physical terms and without reference to their symptoms. Psychogenic disorders belong to a different category of causation, which cannot be adequately described without using psychological terms or bringing in their symptoms.

This, of course, does not exclude the possibility that more than one type of causation may be operative in the same patient at the same time. For example, an individual's abnormal psychological reactions to past experiences may be explicable in psychological terms, but they may also be the result of an inherited predisposition depending upon the structure and functions of his nervous system. Conversely, a person with an inherited predisposition to recurrent attacks of depression, which presumably depends upon some abnormality in the behaviour of his nervous system, may have an attack of depression precipitated by some psychological stress. And it is still very difficult in the present state of our knowledge to evaluate the relative importance of physical and psychological factors in the causation of some psychological disorders, of which the obsessional states are a good example.

Hence a patient suffering from a psychological disorder needs to be considered from both neurological and psycho-

logical standpoints. In practice, in spite of the need for this dual approach and the frequent interaction of the two modes of causation, in many patients the physical or the psychological element will clearly predominate, and this will determine the method of treatment.

It seems to me to follow, from what I have said, that even if by neuropsychiatry is meant only the field common to both medical neurology and psychiatry, it is impossible for a single practitioner to be expert in all parts of it. But, even so, it does not follow that the present division between the two subjects is made in the right place. This is the outcome partly of historical and partly of social considerations, the need for the segregation of some of the mentally ill having in the past isolated in mental hospitals patients suffering from certain neurological disorders and from mental illnesses the causation of which was, and is still, unknown. Neurology grew up in equal isolation from the mental hospital, and the study of the psychological effects of cerebral lesions, however interesting to neurologists and psychologists, seemed to have little to contribute to the understanding of the major psychiatric problems of schizophrenia, cyclophrenia, and the depressive states. The theory and practice of analytical psychopathology and psychotherapy were developed largely in isolation from both neurology and mental hospital psychiatry. Fortunately these barriers are in many places being steadily broken down.

Neurology and General Medicine

The Committee on Neurology of the Royal College of Physicians of London made the following statement: "Neurology remains a part, though an important part, of general medicine and cannot without danger to its own vitality allow itself to become separated from the larger whole. Much of the most valuable neurological material is to be found in the general medical and surgical wards and out-patient departments. Many neurological disorders are the direct result of disease of the cardiovascular system. Others are as directly related to general or local infective processes or to disorders of nutrition or metabolism." The Committee drew from this the conclusion that "to be able to play his part fully in the recognition and management of such cases, it is essential that the neurologist should base his specialized knowledge on a foundation of sound training and experience in general medicine and on a general familiarity with allied specialties such as is obtainable in a large general hospital.

I think that the facts to which the Committee drew attention imply not merely that the neurologist should "base his specialized knowledge on a foundation of sound training and experience in general medicine," but also that there should be a close continuing relationship between neurology and general medicine in the work of our hospitals. No branch of medicine can live on its past achievements, and, although the sphere of applied anatomy and physiology which has yielded such a rich harvest to neurology in the past is by no means exhausted, it may well prove to be subject to a law of diminishing returns, while fresh fields await cultivation. Nothing can take the place of the special neurological hospital. It has an essential part to play in the training of neurologists and provides a unique forum for the interchange of ideas and a continuing stimulus to the thought of the neurologist already in practice. Moreover, it is also the most suitable place for the expansion of neurology into some of the new fields which recent scientific developments, especially in biochemistry and electronics, are opening.

In the special hospital, however, there is a relative lack of certain types of clinical material, and it is inevitable that there should be some neurological disorders which are to be found chiefly, if not exclusively, in relation to general medical diseases and not therefore at a special hospital, while much of the neurology of childhood is to be found in children's hospitals. An increasing amount of research work is being done in these fields, and has already demonstrated its value both to neurology and to medicine. This can be developed as it should only if the work of the neurologist in the general hospital is given the fullest possible scope. It would be a mistake to suppose that his place there can be supplied by the general physician. The scope of neurology as outlined in this lecture is surely a sufficient general refutation of that. The recognition of new syndromes requires expert knowledge to differentiate them from other clinically similar conditions or out of what has hitherto been regarded as a homogeneous group of disorders. Similarly the assessment of the indications for therapeutic procedures must in difficult cases depend upon a knowledge of the multiplicity of factors involved which only the expert possesses.

The contribution of the specialist to diagnosis is equally important. We are all of us apt to regard the field of work of others as possibly less complex than our own, and there exist physicians who, though well enough aware of the complex effects of disturbances of suprarenal function, regard the diagnosis of paraplegia as something which presents no great difficulty. The neurologist who is an active participant in the work of his general hospital will do far more than merely help his colleagues with the diagnosis of cases which seem to them difficult; he will educate them in the difficulty of cases which seem to them easy. He also has a valuable contribution to make to medical teaching, since neurology is a subject which lends itself especially to the education of the student in the importance of accurate history-taking, careful clinical examination, and the logical processes by which a diagnosis is reached.

Conclusions

What I have said well illustrates, if indeed it needed to be illustrated, the rich contribution which specialization has made to medicine. To-day, far from knowing more and more about less and less, the specialist, like every one of his colleagues in medicine, needs to know more and more about more and more. Hughlings Jackson said in 1887: "As scientific medical research goes on, there is greater specialization of investigation, just as, in the development of society, there is that continually increasing specialization, called division of labour. This being so, all the more need is there that there should be greater integration, just as along with division of labour there is need for co-operation of labourers." Failing the appearance of a race of medical supermen who can take all medical knowledge for their province, this integration can be accomplished only by the exchange of information between workers in different fields, and this is most easily achieved by enabling them to meet and work together under the same roof.

It is true that the rapid expansion of scientific knowledge in medicine calls for a review of our methods of organization, and possibly, even, for new tools of thought, but, judging by the results so far achieved, there is nothing to suggest that the human mind is anywhere near the limits of its ability to deal with the challenge created by its own productivity. If we ask what part neurology is to play in this process the answer begins to emerge from our survey of the scope of the subject. Neurology plays a part in physiology, psychology, psychiatry, pathology, bacteriology, medicine, surgery, and no doubt other disciplines, and all of these in their turn have a contribution to make to neurology. What, then, is the role of the neurological physician? The fact that he alone is commonly called a neurologist surely reflects his key position in relation to neurology.

The process of integration, to which I have just alluded, is more likely to be successful if there is an integrator; and the neurologist, though he cannot possibly be an expert in all these fields, is the person most fitted by training, experience, and opportunity to be a nodal point in the relations of neurology. Even so, as the College report recognized, within the work of the

neurologist there is room for some differentiation. "In the future, as has always been the case in the past, some neurologists will be particularly interested in those aspects of neurology which are relatively remote from psychiatry. Others will find their chief interest in those neurological disorders in which the psychiatric aspect is prominent. These latter should be in a position to pursue their interests unfettered, for they have a most valuable contribution to make to the study of neurology as a whole, and, especially at a time when psychiatry is turning more and more to physical methods of treatment, they have similarly a valuable contribution to make to the study of psychiatry." The Committee also saw the need for the general physician, who combines an interest and training in neurology with his general medicine. The growing relationship between neurology and general medicine might well now be more widely recognized in the training of the neurologist, as it has been in the arrangement recently entered into between the Maida Vale Hospital and the London Hospital for two alternating senior registrarships tenable at both.

I have been speaking of definitions: let me end with a parable. The Pigeon in *Alice in Wonderland* insisted that Alice must be a serpent because she ate eggs. "'Little girls,' said Alice, 'eat eggs quite as much as serpents do, you know.' 'I don't believe it,' said the Pigeon, 'but if they do, they're a kind of serpent, that's all I can say.'"

The logic of the Pigeon sometimes finds expression to-day. Many kinds of doctors rightly see patients with nervous disorders, but the future of neurology in this country still depends upon its ability to attract, train, and provide satisfying work for *neurologists* of equal calibre to those to whom we owe the achievements of this branch of medicine and science in the past.

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THE CHOLECYSTOGRAM AND THE CLINICIAN*

BY

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The first step to any form of treatment, whether medical or surgical, is to make an accurate diagnosis. The selection of patients for operation is made on clinical grounds and on the results of appropriate technical investigations. The usual investigation to clarify a diagnosis of disorder of the biliary tract is cholecystography. Great reliance has been placed on this type of investigation despite the fact that it gives a positive diagnosis in less than half the cases of suspected disorder of the biliary tract submitted to it. In an analysis of four separate series of 100 consecutive cholecystographic examinations from three hospitals and my own personal series, the numbers of cases in which no abnormality was reported were 56, 55, 66, and 66. This seemed to be a high incidence, particularly as all the patients had definite symptoms of a disorder of the biliary tract which in many cases was severe. The problem that arises is, What is the diagnosis of these patients, and how may the diagnosis be made?

The "classical cholecystogram" will demonstrate the presence or absence of a gall-bladder shadow, it may demonstrate the presence of gall-stones, it may demonstrate morphological abnormalities of the gall-bladder, it may show a subnormal power of concentration, it will demonstrate whether the gall-bladder contracts or not after a fatty meal. It will not give exact information on the evacuation of the gall-bladder, nor will it in any way give information concerning the various motor dysfunctions of the biliary tract. There are also morphological abnormalities which are not demonstrated by the classical method.

Serial Cholecystography

Experience with the technique of per-operative manometry and radiology (Mallet-Guy and Rose, 1956) over the past three years has demonstrated quite decisively the incidence and importance of disturbances of the motor function of the biliary tract—biliary dyskinesia. A dyskinesia was demonstrated in no fewer than 126 cases out of the first 200 consecutive cases investigated and treated during that time. In 38 of these 126 cases there was a dyskinesia in the absence of any morphological abnormality. This experience indicated the necessity for a more accurate pre-operative method of diagnosing dyskinesia. It was thought that cholecystography should be able to provide the answer to this problem. It was also obvious that cholecystography in its usual form did not supply the answer.

Boyden (1926), in his original work, studied the motor function of the gall-bladder by means of a series of cholecystographic pictures, from which he calculated the volume of the gall-bladder and drew a graph of its evacuation. Clinical radiologists abbreviated this method, and the present technique of cholecystography is to take control pictures before the ingestion of an opaque medium, 14 hours after it, and further radiographs at a variable time after a fatty meal. In some departments this refinement is omitted. This abbreviation destroyed in great part the value of

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Boyden's work to the clinician. In 1949 Siffert revived the method and simplified the computation of the volume of the gall-bladder. In succeeding years Busson (1951), Robert, Bugiel, and Olivier (1952), and above all Guy Albot *et al.* (1952, 1954), further elaborated the method but simplified the computation of the gall-bladder volume so that to-day serial cholecystography will give an exact diagnosis of biliary-tract dysfunction provided there is a gall-bladder shadow.

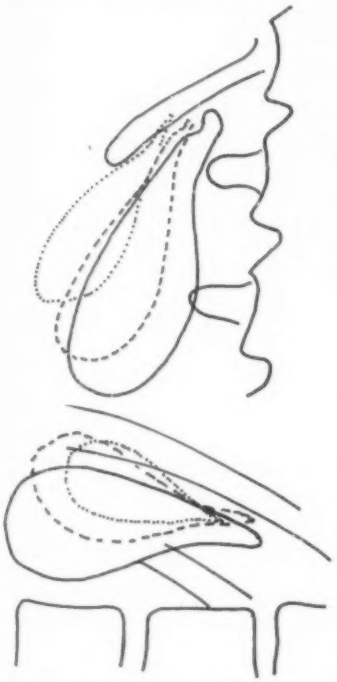

FIG. 1.—Superimposed tracings from a normal serial cholecystogram showing the alteration in the size and position of the gall-bladder shadow, in the two views.

Briefly, the method used is to take both antero-posterior and lateral radiographs 14 hours after the ingestion of a single dose of iopanoic acid ("telepaque") and then every 10 minutes after a fatty meal for 80 minutes (Rose, unpublished). From these radiographs the volume of the gall-bladder is computed and two curves are drawn: the curve of the volumes, and the curve of the angle or erection of the gall-bladder (see Figs. 2–5). This is the angle between the long axis of the gall-bladder and that of the spinal column in the lateral view. This angle is important, as any increase of the angle has the effect of reducing the apparent length of the gall-bladder shadow in the antero-posterior view and so must be taken into account when calculating the volume. Normally it is between 5 and 15 degrees, and it depends on two factors: (1) the tone and force of contraction of the gall-bladder, and (2) the resistance to its evacuation.

After the ingestion of a fatty meal the gall-bladder shadow normally becomes smaller and in the antero-posterior view moves proximally and rotates externally (Fig. 1). In the lateral view the shadow appears to rotate so that the long axis becomes more vertical and the angle of erection increases from 5 to 15 degrees. The normal volume of the gall-bladder is between 25 and 30 ml., and in normal circumstances decreases by 70% in the first 30 minutes after the fatty meal.

In abnormal states the gall-bladder may evacuate insufficiently (hypokinesia) or it may evacuate excessively (hyperkinesia). The gall-bladder tone, as indicated by the angle of erection, may be less than normal (hypotonic) or greater than normal (hypertonic). In conditions of obstruction to evacuation the curve of the angle of erection contrasts strongly with that of evacuation (Fig. 2). The evacuation is insufficient while the angle of erection increases. If, however, the angle of erection is initially low and fails to increase during the test, then the gall-bladder is atonic (Fig. 3). The gall-bladder may evacuate excessively and yet have a small angle of erection which does not increase during the test. This occurs when the sphincters are particularly atonic and the normal stimulus to evacuate, which is hormonal, produces an excessive response.

Personal Series

Between October, 1954, and December, 1956, 200 cases of disorder of the biliary tract were admitted to the clinic for investigation and treatment, but it was not until Case 63 that serial cholecystography was used as a means of selection of cases for operation. Of the other 137 patients, 40 had a normal "classical" cholecystogram, but serial cholecystography showed a dyskinesia which was subsequently proved at operation in each case. The most common finding was a vesicular stasis—that is, a gall-bladder which evacuates insufficiently. There were 34 of these cases.

The gall-bladder may fail to empty normally because of atony of its muscle; there were 20 such cases, 7 of which were also associated with a morphological abnormality. Case 96 is an example.

Case 96.—A woman aged 41 had a history of painful dyspepsia for nine years with invalidism. She had been investigated and treated five times, with negative "classical" cholecystograms, two laparotomies, appendicectomy, and division of adhesions. Serial cholecystography in 1955 showed a gall-bladder of normal size which evacuated moderately insufficiently. The angle of erection was disregarded on account of probable adhesions (Fig. 3). Cholecystographic diagnosis: vesicular stasis probably due to biliary hypotonia. At operation on October 26, 1955, the intravesicular pressure stabilized at 11 cm. of water. Cholecysto-cholangiography showed a distended gall-bladder. Operative diagnosis: biliary hypotonia. Operation: right

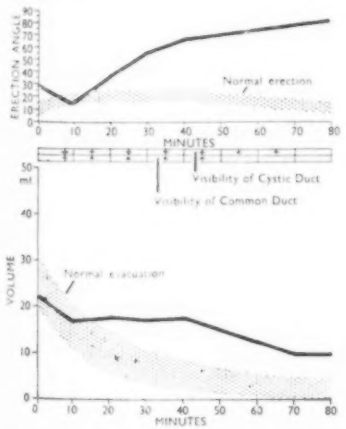

FIG. 2.—Case 221. Serial cholecystogram in a case of obstruction of the cystic duct due to an infundibulo-colic kink.

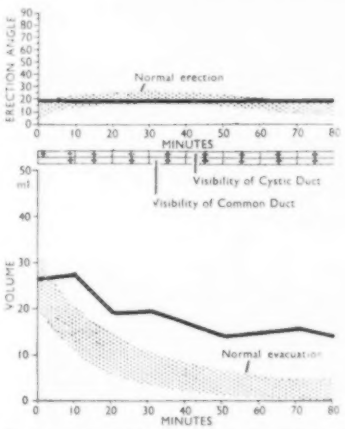

FIG. 3.—Case 96. Serial cholecystogram in a case of vesicular hypokinesia with hypotonia.

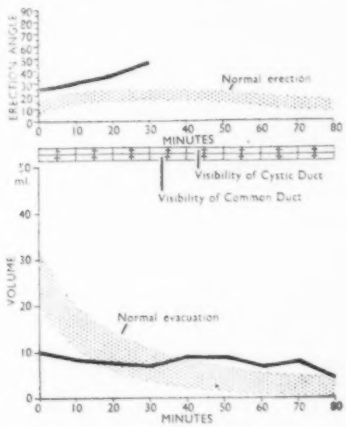

FIG. 4.—Case 180. Serial cholecystogram in a case of obstruction of the cystic duct due to spasm of the sphincter of Lütkens.

splanchnicectomy. Result: there was a considerable amelioration of symptoms and a replacement of 28 lb. (12.7 kg.) of weight loss with a return to full duties.

Of these 20 cases, 13 were unassociated with any morphological abnormality, and only a right splanchnicectomy was performed. Four cases were associated with gall-stones, and in addition to the right splanchnicectomy three had a cholecystectomy and one had a cholecystlithotomy. Two cases were associated with a chronic cholecystitis and one with a cholesterosis; these cases also had a cholecystectomy and right splanchnicectomy. Of the results, 17 were good and three were unsatisfactory.

The gall-bladder may fail to empty normally because of an obstruction to the neck of the gall-bladder or cystic duct due to spasm of the sphincter of Lütkens or to some organic abnormality. There were 14 such cases, and seven were due to spasm of the sphincter of Lütkens, two of which were associated with a duodenal ulcer. Case 180 is an example.

Case 180.—A woman aged 39 had a history of duodenal-ulcer-like dyspepsia with associated biliary symptoms for seven years. Barium-meal examination showed a duodenal ulcer. Serial cholecystography showed a gall-bladder with gross insufficiency of evacuation. There was a steeply rising angle of erection. The antero-posterior view showed a "golf-ball" gall-bladder (Fig. 4). Cholecystographic diagnosis: vesicular stasis from a cystic duct obstruction. At operation on October 1, 1956, an anterior-wall duodenal ulcer was found. The pressure within the gall-bladder was of the obstruction type. Cholecysto-cholangiography showed a small pear-shaped gall-bladder, a normal common duct, but a very long reflux along the duct of Wirsung. After vagotomy and posterior gastro-enterostomy had been performed the intravesicular pressure rose to 15 cm. of water and then stabilized at 12 cm. of water. Operative diagnosis: spasm of sphincters of Lütkens and Oddi and a duodenal ulcer. Operation: vagotomy and posterior gastro-enterostomy. Result: complete cure.

In all these cases a vagotomy was performed and all the results were good.

Seven cases were due to a valve, a fibrosis of the cystic duct, or an infundibulo-colic kink. Case 221 is an example.

Case 221.—A woman aged 30 had a history of painful dyspepsia associated with severe headaches for five years. A serial cholecystogram showed a gall-bladder of normal size which evacuated with moderate-to-gross insufficiency. The angle of erection was of a minus quantity; this minus angle increased considerably during the examination. On the lateral view at 10 to 40 minutes an infundibulo-colic kink was demonstrated (Fig. 2). Cholecystographic diagnosis: vesicular stasis due to cystic duct obstruction. At operation on February 18, 1957, the pressure within the gall-bladder first rose to 20 cm. of water and then stabilized at 12 cm. of water. The cholecysto-cholangiogram showed a marked kink at the infundibulo-colic junction. Operative diagnosis: infundibulo-colic kink; the gall-bladder was on a long mesentery. Operation: cholecystectomy. The pathological specimen confirmed the diagnosis. Result: complete cure.

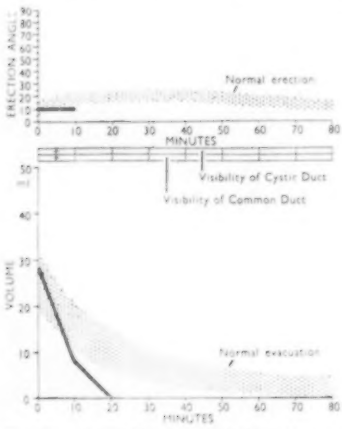

FIG. 5.—Case 204. Serial cholecystogram in a case of vesicular hyperkinesia with hypotonia.

These seven cases all had a cholecystectomy performed, but three of them, being also associated with a biliary hypotonia, also had a right splanchnicectomy; all seven gave good results.

The opposite condition to a vesicular stasis is a gall-bladder which empties too rapidly—a vesicular hyperkinesia. In this series there were six such cases: one was associated with a duodenal ulcer and was treated as a duodenal ulcer; one was treated medically; and two had a chronic cholecystitis which resulted in an irritable gall-bladder, and a cholecystectomy was performed. The remaining two had a marked biliary hypotonia, and a right splanchnicectomy was performed. Case 204 is an example.

Case 204.—A woman aged 67 had a history of painful dyspepsia for twelve years. Serial cholecystography showed a gall-bladder of normal size which emptied rapidly with an angle of erection which did not alter during the examination (Fig. 5). Cholecystographic diagnosis: vesicular hyperkinesia with hypotonia. At operation on January 7, 1957, the pressure within the gall-bladder stabilized at 8 cm. of water. The cholecysto-cholangiogram showed a dilated pear-shaped gall-bladder and a tortuous cystic and common duct. Operative diagnosis: biliary hypotonia. Operation: right splanchnicectomy. Result: complete cure

One of the two cholecystectomy cases was considerably improved and one had a bad result. Of the right splanchnicectomy cases, one was a complete cure and one was considerably improved. The patient with duodenal ulcer was completely cured. The patient on medical treatment was improved but not cured.

Conclusion

It should be noted that not one of these 40 cases would have been either diagnosed correctly or treated successfully without the use of serial cholecystography and peroperative manometry and radiology. Classical cholecystography failed to reveal any abnormality in these cases.

These facts have led me to abandon the classical method of cholecystography in favour of the serial method as a means of selection of cases for operation, when peroperative manometry and radiography will confirm the diagnosis and give the indication for operative treatment. A normal classical cholecystographic report on a patient suffering from symptoms which implicate the biliary tract is incorrect in 95% of cases.

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The Proceedings of the Hastings Conference of the National Society for Clean Air, now available, contain all the papers, lectures, and addresses, together with the discussions, given at the conference, which was held last October. From the viewpoint of fuel policy there is the address by the Minister of Power, Lord MILLS. Two papers discuss the question of air pollution from road vehicles, two more the administrative problems of the Clean Air Act, and others examine the Act from the standpoint of industry and fuel efficiency. There is also a contribution by the Director-General of the Meteorological Office, Sir GRAHAM SUTTON. The Society's president, Dr. R. LESSING, devotes most of his address to a discussion of the means for controlling the primary sources of pollution. There is a short report on the availability of smokeless fuels, and a resolution and statement calling for greater efforts on the part of all concerned to organize the training and certification of boiler operators. The Proceedings are obtainable from the Society, Palace Chambers, Bridge Street, London, S.W.1, price 12s. 6d.

CHRONIC GAMMA IRRADIATION

EFFECTS ON THE PERIPHERAL BLOOD AND HAEMOPOIETIC SYSTEM OF FEMALE GUINEA-PIGS

BY

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Numerous workers have established that chronic *x*- and gamma-irradiation eventually produces anaemia and pancytopenia in all species (Lorenz *et al.*, 1954; Ingram and Mason, 1954), the onset of the anaemia being a late and relatively sudden event. The pathogenesis of this anaemia is not understood. Though marrow studies after death have been carried out (Heineke, 1905; Lorenz *et al.*, 1954; Ingram and Mason, 1954) no serial marrow studies have previously been made.

The present experiment was an attempt to discover by means of serial marrow studies whether the sudden onset of anaemia in chronically irradiated animals was presaged by changes in the marrow and to what extent the changes in the peripheral blood reflected changes in the marrow. Guinea-pigs were chosen, as their haemopoietic system is sensitive to radiation, changes caused by chronic irradiation are clear-cut, and the work of Lorenz *et al.* (1954) has established the dose levels necessary to produce these changes.

Materials and Methods

The female hybrid guinea-pigs used were English short hair, from a partially inbred laboratory stock, weighing 700 to 1,000 g. at the beginning of the experiment. They were irradiated by a ^{60}cobalt source (1.2 MeV gamma rays) at a rate of 10 r per 16-hour day (measured in the empty cage), seven nights a week, irradiation being continued to death.

The guinea-pigs were housed in cages of "nural" aluminium, 23 in. (58 cm.) long, 12 in. (30 cm.) wide, and 12 in. (30 cm.) high; the floors were 18 gauge, and the walls 16 gauge and perforated. Cages were sterilized once a week and the straw bedding changed on alternate days. The animals were fed on a standard diet 18 (Bruce and Parkes), supplemented with hay, cabbage, and water *ad lib.*

Selection and Grouping of Animals.—There were two control groups, each of four unirradiated animals, one group for blood examinations only (group 1) and one for blood examinations and serial biopsy of the marrow (group 2). There were two irradiated groups each of 12 animals, one group for blood examinations only (group 3) and one for blood examinations and serial marrow biopsy (group 4). The animals in the four groups were matched by body weights.

Examinations Carried Out.—Initially the peripheral blood of each animal was examined every 9–10 days, but examinations became more frequent, often daily, as animals approached the critical stage. Marrow biopsies were performed on animals of groups 2 and 4 at intervals of 9–10 days, immediately after blood samples had been taken. Where possible, marrow specimens were also taken on the last day of life of group 4 animals and immediately after death on all animals.

Techniques

Up to 1 ml. of blood was obtained without difficulty by transilluminating the ear and making a small stab incision into a vein; when marrow specimens were required the guinea-pigs were then anaesthetized with intraperitoneal sodium amylobarbitone. For each animal the marrow was obtained from the tibia, femur, and humerus in turn. A hole was drilled in the surgically exposed bone, using a dental drill (flat fish No. 1), and marrow aspirated with a 10-ml. syringe and a No. 0 gauge needle. Skin wounds were closed with Michel clips and covered with a collodion dressing; all healed quickly and cleanly.

Blood examinations included counts of red cells, using the method described by Dacie (1956), red cells showing basophilic stippling and polychromasia, total white cells (Dacie), and differential white-cell counts, counting 200 white cells (Leishman's stain). Packed cell volume was estimated by a microhaematocrit method with Heller-and-Paul mixture as anticoagulant. Haemoglobin was estimated by the oxyhaemoglobin method using an E.E.L. colorimeter. For platelet counts on capillary blood a modification of Brecher and Cronkite's (1950) technique for venous blood was used.

Marrow smears were made on slides and stained with Leishman's stain. Differential counts were carried out on selected smears, and were continued until a minimum of 100 immature leucocytes had been counted. Considerable variation in the amount of marrow obtained and the degree of dilution with peripheral blood was experienced. Marrow in countable quantities was, however, obtained in all instances, though the total number of cells which had to be counted before the target of 100 immature white cells was achieved varied between the wide limits of 600 and 2,000.

Post-mortem examinations were carried out on every irradiated animal and, at the conclusion of the experiment, on four control animals. Marrow smears were made immediately from the right tibia, femur, and humerus, and some of the marrow from these bones was placed in formol-saline for sectioning. The left tibia, femur, and humerus were placed intact into formol-saline for fixation, decalcification, and subsequent sectioning.

Results

Body Weights (Fig. 1, A and B).—While animals of groups 2 and 4 were undergoing marrow biopsies their weights were constantly lower than those of animals in groups 1 and 3, but in group 2 when the marrow biopsies ceased the animals gained weight until their weights equalled those of group 1 animals. The surgical intervention and anaesthesia undergone by the animals of groups 2 and 4 was presumably responsible for these differences in body weights. A further difference in weights is evident between group 1 and

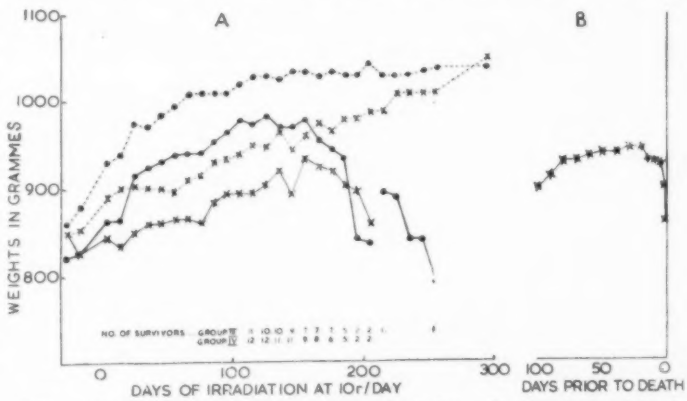

FIG. 1.—A: Mean body weights of female guinea-pigs. B: Terminal weights in group 4. Group 1 ●---●; group 2 ×---×; group 3 ●——●; group 4 ×——×.

group 3 animals and between group 2 and group 4 animals. It seems that irradiation also had some depressive effect upon animal weights, though this effect is less than that achieved by minor surgery and anaesthesia. Sudden loss of weight in irradiated animals occurred only in the last five days of life.

Survival and Death.—The mean survival time for all irradiated animals was 178 days with a mean accumulated dose of 1,780 r. The first death occurred at 114 days (1,140 r) and the last death at 345 days (3,450 r). Of the deaths, 91% occurred between 114 and 205 days (1,140 and 2,050 r). There was no significant difference in the survival times between animals of groups 3 and 4.

Post-mortem Findings and Cause of Death

Haemorrhage varying in degree and distribution was found in every irradiated animal. Ecchymotic and petechial haemorrhages were present in the myocardium and endocardium in 12 instances and in the lungs in 10; in four of the latter pulmonary haemorrhages were extensive. Petechiae, ecchymoses, and/or larger haemorrhages were present in the stomach wall in 15 instances; they were mostly on the anterior surface and greater curvature, and appeared to be submucosal.

Haemorrhages, widespread and varied in distribution, were found in the small intestine in 21 cases; they were not more common at any one site, and the degree of bleeding varied from a few petechiae to, in five instances, extensive massive and recent haemorrhage throughout the whole length of the small bowel.

In 13 animals haemorrhage was found in some portion of the large bowel, the most common site being the caecum and ascending colon. In eight instances the haemorrhage was massive, and in two instances massive submucosal haemorrhages had distended the ascending colon to a diameter of ½ in. (1.3 cm.). In three animals frank bleeding per rectum was seen prior to death.

Subcutaneous haemorrhages, mostly small, were noted in 10 animals. They occurred most commonly in the axillae, neck, anterior abdominal wall, and thighs, and at sites of recent marrow biopsy, where they were more extensive. Petechial haemorrhages were found in mesenteric lymph nodes in six animals, in the suprarenal cortex in four, and their presence was suspected in the livers of some five animals.

Pericardial effusions, varying from slight ones to volumes of 2–3 ml., were found in 13 animals; in 10 instances effusions were blood-stained.

The naked-eye appearance of the marrows in the split long bones varied greatly; in some, both quantitatively and qualitatively, it resembled that of the controls; in others the marrow appeared very pale and fatty. Microscopical examination revealed that the naked-eye appearance gave no indication of the degree of cellularity present.

Apart from undue pallor of the liver and kidneys no other significant abnormalities were found. All animals appeared to be well nourished.

In 10 instances the haemorrhages found at post-mortem examination were extensive enough for this to be regarded as the terminal event, and in three instances haemorrhage was severe enough to be regarded as a major contributory factor.

Peripheral Blood Examinations.—The haematological values for the 32 animals before irradiation were as follows: red-cell count, 4,800,000/c.mm. (S.D. 380,000); packed cell volume, 42% (S.D. 2.2%); haemoglobin, 14.7 g./100 ml. (S.D. 1.17 g.); platelets, 396,000/c.mm. (S.D. 50,000); total leucocytes 10,300/c.mm. (S.D.4,000)—heterophils 3,000/c.mm. (S.D. 1,650), lymphocytes 6,000/c.mm. (S.D. 2,450). Normal mean values for counts of polychromatic cells and stippled cells varied between 0.4 and 0.6%, and 0.5 and 0.15% respectively.

Effects of Repeated Venepuncture.—The mean platelet counts in the control animals varied during the experiment between 350,000 and 420,000 per c.mm. (Fig. 2, A). On the second bleeding there was a drop of some 13% in the mean platelet count, and, whilst a fall of this degree appears to be within the normal variation for the eight control animals, it was also apparent in the irradiated groups, and in these groups it was statistically significant.

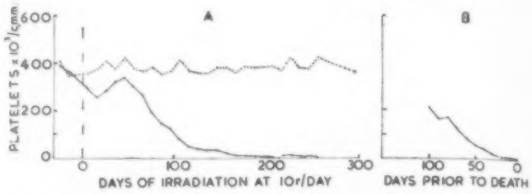

FIG. 2.—A: Mean platelet count of female guinea-pigs. B: Terminal count. Irradiated animals: continuous line. Control animals: dotted line.

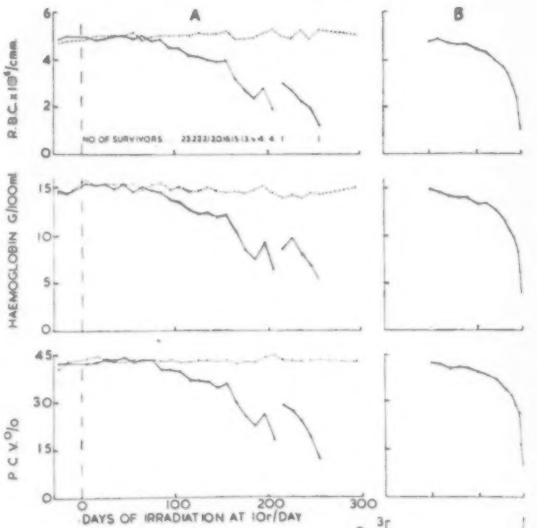

FIG. 3.—A: Mean red-cell counts, haemoglobin, packed cell volumes, polychromasia, and stippled-cell counts of female guinea-pigs. B: Terminal counts. Irradiated animals: continuous line. Control animals: dotted line.

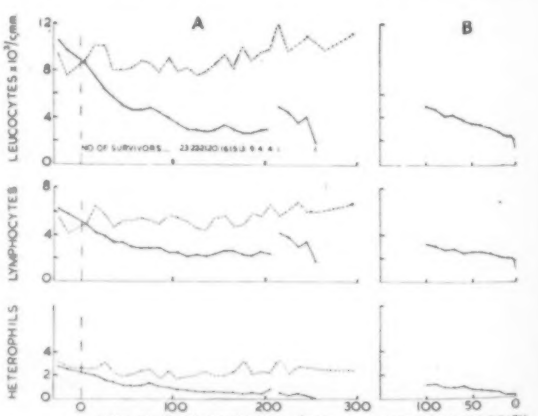

FIG. 4.—A: Mean total and differential leucocyte counts of female guinea-pigs. B: Terminal counts. Irradiated animals: continuous line. Control animals: dotted line.

Effects of Anaesthesia and Marrow Biopsy.—Comparison of findings in group 2 and 4 animals with those in groups 1 and 3 shows no difference in the platelets and red-cell counts at any time, apart from a small transient rise with return to normal values in the number of stippled and polychromatic cells of group 2 animals following each marrow biopsy. After the first 50 days of the experiment the total white-cell counts in group 2 and 4 animals were slightly but consistently higher than in group 1 and 3 animals.

Effects of Ageing (Controls).—During the first 40 days the mean red-cell counts of control animals rose slightly from 4,690,000 to 5,000,000/c.mm., and this was accompanied by a rise in the haemoglobin and packed cell volumes (Fig. 3, A). Thereafter no significant variation in these values occurred. For the first 200 days the mean total leucocyte count varied between 8,000 and 10,000/c.mm., but towards the end of the experiment there was a small rise to between 10,000 and 12,000/c.mm. due chiefly to an increase in the number of lymphocytes (Fig. 4, A). No morphological changes in the leucocytes were seen, and only an occasional immature cell was noted.

Effects of Irradiation

To facilitate analysis, results are presented as mean values of 10-day periods against the total dose of irradiation received by the animals. Differences within these 10-day (100 r) periods are very small and generally insignificant when compared with normal physiological variation and the errors inherent in most of these examinations.

The results in the irradiated animals (groups 3 and 4) are presented from two points of view: firstly, as plotted against the radiation dosage, and, secondly, in relation to the time before death at which changes occurred. Three of the group 4 animals are not included in these latter calculations, as they died from sudden massive intraperitoneal haemorrhage following intraperitoneal injection of anaesthetic. Until the occurrence of these haemorrhages, which must be regarded as being precipitated by the trauma of the injection, these animals had followed closely the overall pattern of response to irradiation.

Changes Related to Dosage

Up to 900 r there was no significant change in the red-cell count, haemoglobin, or packed cell volume of any animal (Fig. 3, A). The lowest and highest doses at which a small fall in all three measurements was seen were 950 r and 1,750 r respectively. Up to a dosage of 1,000 r no significant change was seen in polychromatic cell and stippled-cell counts.

Mean total leucocyte counts fell steeply to 45% of the pre-irradiation count during the first 500 r (50 days) (Fig. 4, A); thereafter the rate of decline lessened and levels reached 30% of the pre-irradiation count at 1,100 r (110 days). Individual animals displayed considerable variation in the pattern of fall; in the majority it followed the mean curve, but in some the manner of fall more closely resembled a straight line. By and large, the differential counts paralleled the total counts, though, initially, granulocyte counts fell slightly more rapidly than did lymphocyte counts (Fig. 4, A). Foà-Kurloff cells disappeared proportionally with lymphocytes, and the distribution of eosinophils and basophils followed the general pattern.

The platelet count fall, which occurred between the first and second pre-irradiation bleedings, continued for 15 days (150 r) to reach a mean value of 65% of normal (Fig. 2, A). Platelet counts then rose steeply with, in individuals, a wide variation in the degree and a slight variation in the timing of the rise. The mean peak of rise reached 83–84% of the pre-irradiation count between 40 and 50 days (450 and 500 r). The highest peak was 137% of the pre-irradiation count, and no significant rise was seen in three animals. From 50 days (500 r) onwards mean platelet counts fell sharply and continuously without any secondary rises.

Changes Related to Time Prior to Death

The first indication of irradiation damage seen in the red-cell count and packed cell volume was a fall which in most instances continued precipitately to the moment of death; occasionally this fall was interrupted by a minor rise. The average time between the initial fall and death was 33 days, the shortest time being 15 days. Terminal red-cell counts varied between 1,500,000 and 500,000/c.mm. (Fig. 3, B).

From about 35 days before death the mean corpuscular volume rose from a normal 86–88 cubic microns to 110 cubic microns seven days before death; the mean corpuscular haemoglobin rose from a normal value of 30 γγ to 36 γγ terminally. The normal mean corpuscular haemoglobin concentration remained unchanged between 34 and 35%.

Associated with the macrocytosis the percentage of polychromatic cells rose from a normal value of 0.5% to 2.4% at two days before death, and by the day of death to 3.1% (Fig. 3, B). Similarly, the stippled-cell count rose from a normal value of about 0.1% to 1% at two days before death. As the steady rise in the stippled-cell count occurred the granules were seen to become coarser, with a tendency to clump.

The mean leucocyte count was 49% of normal at 100 days before death; it fell evenly, virtually in a straight line, to 24% of normal at five days prior to death. A further steep fall then occurred to a terminal mean value of 15% of normal (Fig. 4, B).

Complete agranulocytosis was not uncommon, the mean granulocyte count being some 10% of normal. The mean terminal lymphocyte count was 20% of normal, but in individuals this varied between 11 and 42%.

The mean platelet count (Fig. 2, B) was 100,000/c.mm. some 55 days prior to death; it fell steadily; and in most animals thrombocytopenia (30,000 platelets/c.mm. or less) was present by 22 days before death. Terminal counts were much lower than this.

Normal Bone-marrow Differential Count (Expressed as Percentage of Total Nucleated Cell Count and Also as Percentages of Total Immature Cell Count)

Cell Type		Mean (%)	Range (%)
Reticulum and primitive undifferentiated cells		0·3 (1)	0·0–0·8
Myeloid		48·4 (48·1)	
Myeloblasts		0·7 (2·3)	0·0–1·5
Myelocytes	Heterophil	3·5	1·0–6·8
	Eosinophil	1·5	0·1–3·2
	Basophil	0·5	0·0–2·0
	Total	5·5 (17·7)	1·6–10·0
Metamyelocytes	Heterophil	5·6	2·7–11·3
	Eosinophil	2·4	0·2–6·0
	Basophil	0·7	0·2–2·3
	Total	8·7 (28·1)	3·6–13·0
Mature granulocytes	Heterophil	29·0	20·0–45·6
	Eosinophil	3·5	0·7–6·0
	Basophil	1·0	0·2–2·3
	Total	33·5	25·7–40·0
Lymphocytes		13·8	5·0–30·0
Foà-Kurloff cells		0·8	0·0–2·0
Monocytes		0·8	0·0–2·0
Plasma cells		0·4 (1·3)	0·0–1·0
Erythroid		15·2 (49·0)	8·0–26·0
Early normoblasts		2·2	0·4–5·0
Intermediate normoblasts		12·0	7·5–20·0
Late normoblasts		1·0	0·0–3·3
Megakaryocytes*		0·2 (0·6)	0·08–0·8
Damaged cells		20·0	10·0–35·0
Cells in mitosis (per 100 nucleated cells)		1·0 (3·0)	0·4–1·9

* Megakaryocytes were included in the differential count, but, as they were relatively scanty, an attempt was made to assess any change in their numbers during the course of the experiment by counting the numbers present in 100 microscope fields, using a × 5 eyepiece and × 50 objective (magnification × 400), counting along both edges of the film from its thickest part towards the tail. From counts of nucleated cells in several such fields an estimate of the total nucleated cells in 100 fields was made and the megakaryocytes expressed as a percentage of the total nucleated cell count. The normal mean megakaryocyte count by this method was 0·25%, the range being 0·08 to 0·8%.

Marrow Biopsies

The normal mean differential count of marrow cells obtained from the four control group 2 animals and the pre-irradiation counts in the 12 group 4 animals is presented in the accompanying Table. The figures in brackets show these marrow cell counts expressed as a percentage of the total immature cell count and present an attempt to reduce the error caused by dilution of the marrow with peripheral blood mature white cells.

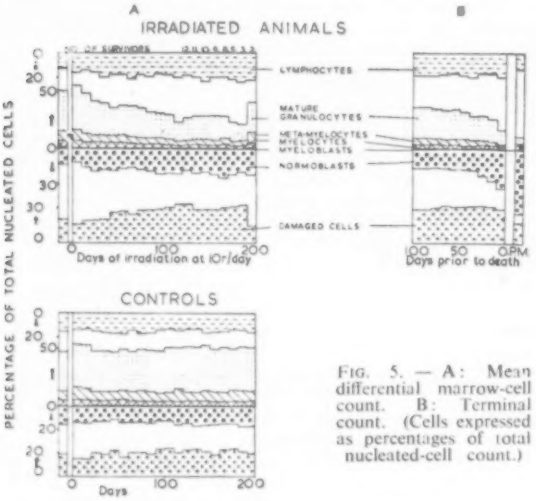

FIG. 5. — A: Mean differential marrow-cell count. B: Terminal count. (Cells expressed as percentages of total nucleated-cell count.)

Effects of Anaesthesia and Repeated Marrow Biopsy (Group 2)

No significant variation from the normal values, as shown in the Table, was encountered throughout the experiment, and it is inferred that multiple serial biopsies do not affect the marrow picture (Fig. 5, A).

Effects of Irradiation—Changes Related to Dosage (Group 4)

From 100 to 1,000 r (10 to 100 days) the proportion of myeloid cells dropped steadily whilst that of the normoblasts rose; the former fell from a normal mean value of 50% to 28% and the latter rose from a normal mean value of 14% to 20% of the total nucleated cell count (Fig. 5, A). These changes in values for immature white and immature red cells become more pronounced when these cell counts are expressed as a percentage of the total immature cells (Fig. 6, A).

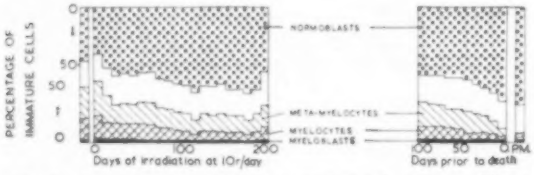

FIG. 6.—Left: Mean differential marrow-cell count. Right: Terminal count. (Cells expressed as percentages of immature-cell count.)

The drop in the myeloid cells was apparent at all stages of development from myelocytes to mature cells and the normal ratio of myelocytes: metamyelocytes: mature granulocytes (16:26:100) was remarkably constant throughout. The rise in the normoblasts was apparent at all stages of development, with a persistence of the normal ratio of early: intermediate: late of 118:100:8.

During the first 1,000 r of irradiation, lymphocyte-type cells (including Foà–Kurloff cells) increased from a normal mean value of 14% to about 20%, the number of damaged cells in smear preparations increased from a normal mean value of 20% to approximately 30%, and plasma cells steadily increased from a normal mean value of 0.5% of the total nucleated cell count to 2%.

After 400 r (40 days) megakaryocytes had increased from an initial mean of 0.26% to 0.37%. This rise was followed by a sudden drop to 0.18% at 600 r and thereafter a constant fall to approximately 0.1% at 1,000 r, and subsequently a complete disappearance.

There was no significant change in the number of cells showing mitosis during the period of irradiation, the normal value of 2–3 per 100 immature cells remaining unaltered.

Effects of Irradiation—Changes Related to Time Prior to Death (Figs. 5, B, and 6, B)

From 100 to 10 days before death the myeloid cells fell from 35 to 16% of the total nucleated cells. This fall was evident at all stages of development beyond the myeloblast stage. At post-mortem examination, however, the total myeloid elements (10.5%) consisted of 1% blast cells, 2% myelocytes, 2.5% metamyelocytes, and 5% mature granulocytes, revealing a radical alteration in the proportion of developing cells with a marked fall in the number of mature cells relative to the metamyelocytes.

During the last 100 days of life the lymphocyte count remained relatively constant at approximately 20% of the total nucleated cells. Foà–Kurloff cells decreased to 0.1% at death. In post-mortem smears lymphocytes were present in approximately normal proportions, the mean figure being 13% of the total nucleated cells. Whilst the damaged-cell count was constant during the last 100 days of life, in post-mortem smears it had fallen to 18% of the total nucleated cells.

Normoblasts, expressed as a percentage of the total nucleated cells, showed a steady increase from 20% at 50 days before death to 33% during the last 10 days of life. In post-mortem smears the mean normoblast count was 56%, and in some marrows normoblasts were the only recognizable cells. The ratio of early, intermediate, and late normoblasts remained constant throughout.

In the period from 100 to 10 days before death the fall in the myeloid cells and the rise in the normoblasts became much more pronounced when these cells were expressed as a percentage of the total immature cells; thus the former fell from 33% to 13% and the latter rose from 59% to 84%. In post-mortem smears the myeloid cells were some 9% of the total immature cells.

In the last 50 days of life megakaryocytes disappeared altogether; not one megakaryocyte was seen in some 80 marrow specimens examined. In post-mortem smears only two megakaryocytes were found in marrow specimens taken from 20 animals.

Post-mortem Smears and Longitudinal Sections of Long Bones

An attempt at a rough assessment of total marrow cellularity from examinations of the longitudinal sections was made (Fig. 7). In 30 oil-immersion fields, distributed uniformly throughout the heads and shafts of the bones, all nucleated cells were counted, mean values of total cellularity were calculated for each animal and expressed as a percentage of the mean values for the control groups. Mean figures for control animals were 270 nucleated cells per field for group 1 and 280 for group 2 animals, with remarkable consistency in individual animals within the group. Mean value for irradiated animals was 121 (44%) for group 3, with a range of 16 to 100%, and 125 (45%) for group 4, with a range of 13 to 91%. Of the 21 animals, 3 had values of 30% or less, 15 had values between 31 and 60%, and 3 had values between 70 and 100%.

Differential counts in post-mortem marrow smears in irradiated animals showed a complete reversal of the myeloid: erythroid ratio found in control animals (Fig. 8). In the pre-irradiation marrow smears of all animals the mean ratio of myeloid cells, immature and mature, to

erythroid cells was 3:1. In the post-mortem smears of the sacrificed control animals the ratio was 3.5:1, whilst in the irradiated animals it was 1:5.2.

Comments

The findings in the peripheral blood studies in this experiment confirmed the following findings of Lorenz *et al.* (1954) in guinea-pigs undergoing chronic irradiation at similar dose levels: (*a*) Severe anaemia of sudden onset is a terminal event. (*b*) Whilst the depression in leucocyte counts is due partly to a decrease in the number of lymphocytes it is due much more to a severe reduction in the heterophil numbers, and profound neutropenia is characteristic of the terminal picture.

The pattern of platelet response—namely, a fall in the platelet count from the beginning of irradiation and the statistically highly significant return to almost normal values between 40 and 50 days—is not understood at present; it might be due to early capillary damage followed by a functional (? physiological) stimulation of platelet production. Though it has not been reported by any other workers using experimental animals, it has been a constant feature of a follow-up experiment which is continuing, and a somewhat similar response was observed in the inhabitants of the island of Rongelap (United States Atomic Energy Commission, 1956).

Though examinations of marrow smears at regular intervals show gradual and progressive changes in the differential picture, these examinations give very little hint of impending disaster except terminally. Furthermore, though in some animals marked falls in the myeloid cell counts and rises in normoblast counts were observed earlier, in others normal values were found within 30 days of death and in two instances were still present at death. It is concluded that neither single nor repeated marrow smears can be relied upon to indicate the degree of irradiation injury or the imminence of the terminal stage.

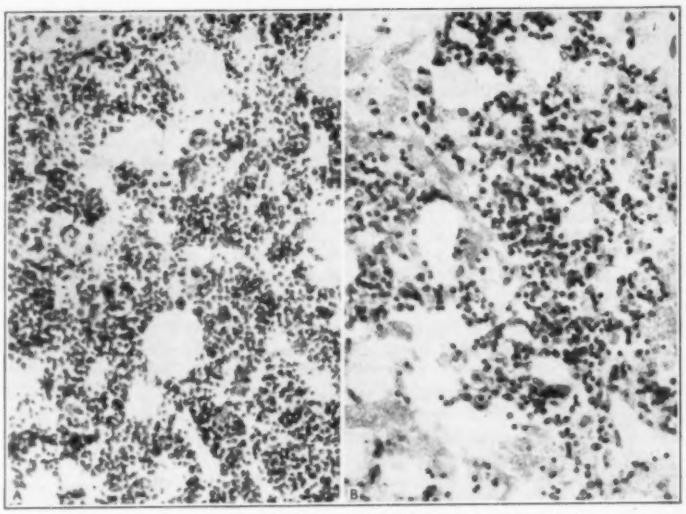

FIG. 7.—Photomicrographs of sections of guinea-pig long bone. A: Control animal. B: Irradiated animal.

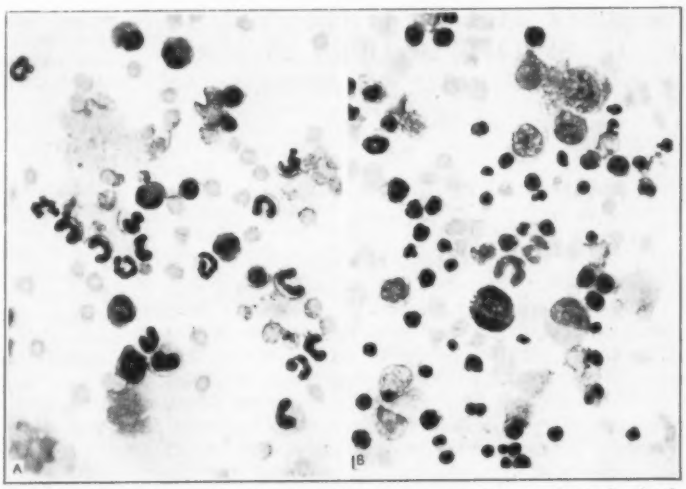

FIG. 8.—Photomicrographs of guinea-pig marrow smears. A: Control animal. B: Irradiated animal.

The complete reversal in the normal ratio of mature and immature myeloid cells to immature erythroid cells found in the post-mortem marrow smears of irradiated animals clearly indicates a far greater sensitivity of immature white cells as compared with immature red cells to this method of irradiation; it may also suggest a relative insensitivity of immature red cells to this level of chronic gamma irradiation.

The absence of any alteration in the early, intermediate, and late normoblasts ratio indicates no maturation defect in cells of the erythroid series.

Post-mortem bone section of irradiated animals shows a reduction in the total marrow cellularity of some 45% of control values, and it seems that this 55% fall can be accounted for entirely by the disappearance of the immature white cells.

The above findings indicate no failure of erythropoiesis or of maturation of the red cells, nor, in this experiment, was there any evidence of increased haemolysis or intravascular destruction of red cells as suggested by Lorenz *et al.* In the majority of animals the post-mortem findings of large haemorrhages, coupled with the fact that entry into the terminal stage never occurred before the platelet count had fallen to critical levels, justify the statement that death was due to anaemia consequent upon thrombocytopenia and haemorrhage.

It is possible that, prior to their precipitate fall, red-cell counts were sustained at an artificially high level by fluid loss with haemoconcentration, but, as up to death the animals maintained a high food and fluid intake and at post-mortem examination appeared to be well nourished, this seems unlikely.

Summary

In hybrid female guinea-pigs irradiated at 10 r per 16-hour day to death, peripheral blood examinations reveal evidence of irradiation injury in the total white-cell counts and platelet counts; only terminally is any significant change encountered in the erythrocyte evaluations.

A hitherto unreported pattern of platelet response is reported.

Neither single nor repeated marrow smears give a reliable indication of the degree of irradiation injury or the imminence of death.

No failure of erythropoiesis or erythrocyte maturation was observed.

It is claimed that death is due to anaemia consequent upon thrombocytopenia and haemorrhage.

I wish to acknowledge my indebtedness to Dr. J. F. Loutit, Director of the M.R.C. Radiobiological Research Unit, who suggested this investigation and provided facilities for its execution; to Dr. R. H. Mole, M.R.C. Radiobiological Research Unit, for many helpful suggestions and much valuable criticism; and to Sick-Berth Chief Petty Officer J. E. Morris, without whose unflagging energy, great zeal, and technical excellence much of this work could not have been completed. Finally, I wish to thank the Medical Director-General of the Royal Navy for permission to publish this paper.

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SCHULTZ–DALE TEST FOR DETECTION OF SPECIFIC ANTIGEN IN SERA OF PATIENTS WITH CARCINOMA

BY

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The search for a reliable and easily performed serological test for carcinoma has interested many investigators for over 60 years, and the number of publications on the subject now runs into several thousands. Homburger (1950) reviewed over 60 tests described in the last 35 years, and none conformed to the strict criteria laid down by Dunn and Greenhouse (1950) of 90% accuracy in cases of cancer, 95% accuracy for patients with non-cancerous disease, careful selection of cases and controls for testing, need for reproducibility in different hands, knowledge of the extraneous factors affecting the cases, and sufficient numbers tested to be statistically significant. Many people feel that it is unscientific to search for a serological test for cancer on account of the diversity of causes and types, and there is no doubt that finding a suitable test is made more difficult by lack of a full knowledge of the cause of human cancer. With other diseases the discovery of the aetiological agent has usually been followed by a simple serological diagnostic test—for example, Widal test, etc.—and it is reasonable to hope that cancer might similarly produce some constant and specific change in the serum which would prove of diagnostic value. Greenstein (1954) has said, "Tumours tend chemically to resemble each other more than they do normal tissue or than normal tissues resemble each other."

A test for carcinoma described by Makari seemed to fulfil the criteria of Dunn and Greenhouse with the exception of information about reproducibility by other workers; furthermore, it was based on two assumptions which it seemed reasonable to make (Makari and Huck, 1955). These are as follows.

1. Any carcinoma in the body will release into the circulation a substance specific to carcinoma tissue and not found in normal patients, probably a molecule or part of a molecule making up the substance of the tumour itself. It has been shown that this is indeed so by Mann and Welker (1940, 1943), who stated that the "proteins of carcinoma tissue may appear in the blood stream and be detected by the appropriate antiserum."

2. It is possible to produce a reaction between this unknown substance and antibodies in a guinea-pig which has been injected with carcinoma. As mentioned above, Mann and Welker (1940, 1943) were able to detect an abnormal substance in cancer sera by using antibodies and a precipitin reaction.

Makari's methods consisted in using one of the most sensitive methods for detecting antigen—the Schultz–Dale bath. He tried several antigens from carcinoma tissue for sensitizing guinea-pigs; the most successful of these gave 96.8% positive results in proved carcinoma and only 4.8% false positives in non-cancerous lesions.

It is the purpose of this article to show that with some modification we have been able to confirm and slightly improve upon these results in a much larger series.

Method

The technique of performing the test was substantially the same as that used by Makari: the only material used for sensitizing guinea-pigs was the one Makari found to give the best results. This fraction was obtained by making a 20% aqueous emulsion of any carcinoma, centrifuging at 3,200 r.p.m., equivalent to an R.C.F. of 1.5 kg./*g*, and then recentrifuging the supernatant at 4,000 r.p.m., equivalent to an R.C.F. of 2.3 kg./*g*; the deposit was then injected subcutaneously in Freund's adjuvant into virgin guinea-pigs, 200–600 g. in weight. This has the effect of removing to some degree the non-specific normal fibrous tissue, blood, and blood vessels. Many differing types of carcinoma, including metastases, were investigated. Those actually used were: adenocarcinoma of breast; adeno-, squamous-, and oat-cell carcinoma of lung; adenocarcinoma of rectum, colon, stomach, and prostate; hypernephroma; chorion-epithelioma; and glioblastoma.

One month later the guinea-pigs were killed and the uterine horns suspended in a Schultz–Dale bath. The horns were desensitized to normal elements in plasma by the addition of 1.5 ml. of normal plasma, until no further contractions were recorded, washing the uterus and allowing it to relax fully between each contraction. 1.5 ml. of test serum was then added to the immune horn and a normal horn. If the patient had a carcinoma the immune horn should have contracted, but not the control one. The criterion accepted by Makari for a positive test was one which gave a contraction which was at least one-fifth the size of that produced by 10 μg. of histamine phosphate. In this work this criterion was found to be adequate, for, though the test was not an all-or-nothing phenomenon, the positive sera generally produced a big contraction, and had the standard been one-third or one-tenth it would have made little difference to the results.

Two modifications of Makari's technique were made. (1) It was found that the uteri of guinea-pigs lost their contractibility in the winter. This was restored by five injections of 0.2 mg. of oestradiol benzoate subcutaneously at three-day intervals before sacrifice. (2) It became obvious early in the work that a large proportion, 30–40% of guinea-pigs, did not become adequately sensitized, sometimes to the carcinoma element only, sometimes to the normal elements as well, and so when a negative result was obtained with a test serum, serum from a patient with proved carcinoma which had previously given a positive test was added to the uterus. If there was still no contraction the uterus was regarded as inadequately sensitized and the result disregarded.

Results

Of the 301 patients with carcinoma tested, 291 were positive (Table I), an accuracy of 96.7%. The 10 false negatives were: early squamous carcinoma of tongue, carcinoma of thyroid, astrocytoma, post-cricoid squamous carcinoma, malignant melanoma with secondaries in brain, malignant carcinoid ?, adenocarcinoma of pancreas with secondaries in liver, primary squamous carcinoma of larynx, adenocarcinoma of breast with secondaries in axillary glands, secondary adenocarcinoma (unknown primary).

TABLE I.—*Results in 291 Cases of Carcinoma*

Carcinoma	Primary Only	Metastasis	Recurrence	Total
Adenocarcinoma of breast	22	11	9	42
Cerebral tumours				37
Carcinoma of lung (all histological types)	15	20	1	36
Adenocarcinoma of stomach	13	10		23
,, prostate	4	16		20
,, colon	13	5	1	19
,, rectum	10	5		15
Squamous carcinoma of skin	10	1		11
Carcinoma of cervix	6	3		9
Transitional cell carcinoma of bladder	9			9
Carcinoma of larynx	5	3		8
Squamous carcinoma of tongue	8			8
Adenocarcinoma of ovary	5	2		7
Squamous carcinoma of oesophagus	4	3		7
,, ,, vulva	6			6
Adenocarcinoma of pancreas	4	2		6
Carcinoma of thyroid	5			5
,, pharynx	4			4
Basal-cell epithelioma	4			4
Malignant melanoma	2	2		4
Adenocarcinoma of body of uterus	4			4
Carcinoma of lip	3			3
Seminoma testis	1			1
Chorionepithelioma of testis	1			1
Hypernephroma	1			1
Squameus carcinoma of anus	1			1

TABLE II

Patient's Condition:	No. Tested
Normal	20
Sarcoma (leiomyosarcoma 5, lymphosarcoma 4, reticulum-cell sarcoma 3, fibrosarcoma 2, liposarcoma 1, osteogenic sarcoma 1)	16
Nephrosis	13
Cerebral thrombosis	12
Molloscum sebaceum	10
Recent coronary infarction	10
Leukaemia	9
Congestive heart failure	9
Normal pregnancy	8
Peptic ulcer	8
Hypertension	6
Active pulmonary tuberculosis	6
Syphilis	5
Disseminated sclerosis	5
Pneumonia	5
Jaundice	4
Multiple myeloma	3
Rheumatic heart disease (without congestive failure)	3
Increased intracranial tension (no malignant cause found)	3
Psoriasis	3
Pituitary adenoma	3
Neurofibroma	2
Infarct lung	2
Cystic mastopathy	2
Abdominal adhesions	2
Fibromyomata uterus	2
Diabetes	2

One each of the following was tested—Lupus erythematosus, brachial neuritis, brain abscess, chronic cervicitis, cystitis, alcoholic patient, after repair operation, mesothelioma pleura, subdural haematoma, exfoliative dermatitis, metropathia, oesophagitis, sebaceous cyst, Simmonds's disease, polycystic kidneys and hypertension, recurrent desmoid tumour of abdominal wall, simple ovarian cyst (serous), basal-cell papilloma, leuco-erythroblastic blood dyscrasia, muscular dystrophy, Hodgkin's disease, leucoplakia of vulva, non-specific granuloma dermis, malaria, teratoma of ovary, tabes, migraine headache.

Of the 207 patients without carcinoma tested, 200 were negative (Table II), an accuracy of 96.7%. The seven false-positive results were: simple gastric ulcer, chronic granulomatous lesion of breast, infarct of brain, and four cases of nephrosis.

Ten carcinomas were tested before and three weeks after removal: 6 were adenocarcinomas of breast, 2 were adenocarcinomas of rectum, and 2 were meningiomas. These cases were chosen because so far as could be ascertained all the growth had been removed and there were no metastases, and four months later they were still free of recurrence. Of the eight carcinomas of breast and rectum, five had become negative and three were still positive. The two meningiomas were still positive, but on testing them two months later they had become negative, as had the other three positive cases.

Seven carcinomas were successfully removed but not tested prior to removal. The length of time since removal was:

Squamous carcinoma of oesophagus	7 years
Adenocarcinoma of uterus	6 ,,
,, colon	6 months
Squamous carcinoma of lung	3 ,,
,, ,, larynx	6 weeks
Adenocarcinoma of breast	3 ,,
Meningioma	3 ,,

The only extraneous factor which appeared to influence the result of a test was haemolysis in the serum, which tended to produce a false-positive result; other factors such as keeping several days at room temperature or several months at −40° C. had no effect on the result.

Makari stated that if he placed a normal uterus in serum containing antibodies to carcinoma then the muscle adsorbed the antibodies and was as suitable for testing as the uterus from the primarily sensitized guinea-pig. This was not confirmed, and on studying Dale's (1913) original article it was seen that this was also what he found, but for some reason or other he was able to sensitize passively in this way muscle which had previously been actively sensitized and subsequently desensitized.

Sarcomas.—When it was noted that a positive test was not elicited with sarcomatous sera it was important to discover if sera from patients with sarcoma would produce a positive reaction when tested in guinea-pigs sensitized to sarcoma; so a reticulum-cell sarcoma, a lymphosarcoma, a fibrosarcoma, and a leiomyosarcoma were extracted in the same way as the carcinomas, injected into guinea-pigs, and tested in the Schultz-Dale bath. It was not possible to produce one positive result from 12 sera from different patients with sarcoma and five patients with leukaemia. This is peculiar in view of the specificity of the test for carcinoma and there is no obvious explanation for it.

Discussion

Quantitative Aspects.—The test has not been found to be a useful quantitative measurement of the amount of tumour present in the body, for it was found that small carcinomas often produced as large a contraction as serum from a patient with a large bulk of tumour. The test therefore is of no value in assessing the amount of carcinoma present in a patient, and no attempt has been made to carry it further than to elicit a positive or negative result. This is understandable, as the size of contraction is dependent on two factors: one is the amount of abnormal substance released from the tumour, which will depend on many different facts as well as size—for example, the degree of differentiation, vascularity, necrosis, and the organ in which the tumour is growing. The other more important factor is the amount of antibody present in the uterus; this is very variable.

It is important to know how small a tumour the test will reasonably detect. This was readily seen in the studies of small visible tumours—for example, skin, lip, and tongue. In this group the test was found to be very accurate down to tumours of ½ in. (1.3 cm.) in diameter. When they were smaller accuracy decreased, and very small squamous carcinomas and basal-cell epitheliomas were negative. This means that the test is valueless in detecting small areas of malignant change—for example, in a polyp or leukoplakia; neither can a good prognosis be given merely because the test becomes negative post-operatively. It is also of importance to realize that a negative result may not become established till some weeks after operation.

False Negatives.—The squamous carcinoma of the tongue and larynx were both small tumours with no invasion or

metastasis, and they both had a strikingly large number of inflammatory cells, particularly plasma cells round the tumour. It may be that these plasma cells were producing antibodies to the tumour and were neutralizing any abnormal substance released from it. The carcinoma of the thyroid was a very well differentiated tumour and might well have been called a benign adenoma but for an area of venous invasion. The astrocytoma was also a well-differentiated and slowly growing tumour, and it may be that these latter two tumours were not dedifferentiated enough to release a substance specific to carcinoma and were chemically more akin to benign tumours, but it should be noted that many well-differentiated carcinomas did give positive tests. The case of carcinoid tumour is the only tumour which was not histologically proved, but it has been accepted as such on the serological levels of 5-hydroxy-tryptamine and the clinical findings. With this in mind it is possible that there might be a reasonable explanation for five of the false negatives.

False Positives.—The fact which stands out is the high percentage of false positives in patients with nephrosis. There are many explanations of this finding, including the possibility of antidiuretic hormone causing a non-specific contraction, but it should also do so in the non-sensitized horn ; or there may be a substance in the serum of nephrosis similar to that found in carcinoma serum which is responsible for the positive reaction. In the course of this work chromatographic investigations of urine of patients with nephrosis and carcinoma (Burrows and Neill, 1958) suggest that this may be so. So far there is no satisfactory explanation.

Probably no serological test for cancer will ever be of use for screening large normal populations, on account of the large number of normal people who would have positive tests and have to be investigated for cancer, and this test is no exception. Where it has been found of great value is in the study of patients in whom a question of carcinoma is raised in diagnosis ; but the most valuable aspect of the test has been in assessing patients who have had a carcinoma removed some time previously and have returned complaining of symptoms which could mean recurrence of the original growth. All patients in this group gave a positive result.

Summary

A test described by Makari and Huck for serological diagnosis of carcinoma has been investigated. There was 96.7% accurate diagnosis in 207 patients with non-carcinomatous disease and 96.7% accurate diagnosis in 301 cases of histologically proved carcinomas.

The use and limitations of the test are discussed.

My thanks are due to Professor J. H. Biggart for his help and advice with this work, and to the consultants of the Royal Victoria Hospital, Belfast, who made available their patients for study.

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INVESTIGATION OF THE IMMUNOLOGICALLY ACTIVE CONSTITUENT OF SERUM OF PATIENTS WITH CARCINOMA

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The demonstration in the serum of patients with carcinoma of the presence of a substance capable of initiating contractions in the immune guinea-pig uterus suggested a study of such sera to elucidate its nature. In the absence of any information on its structure beyond its immunological similarity to some component of the carcinoma itself an attempt was made to separate suitable sera on the basis of physical or chemical properties and to test each of the separated fractions for specific activity in the Schultz-Dale bath. Although a number of fractionation techniques were used it was found that in most cases efficient separation was achieved only at the expense of partial denaturation of the protein constituents of the serum. Paper electrophoresis did, however, achieve reasonably good separation of the serum proteins without degradation, and apparatus was set up to achieve separation on a preparative scale by the technique of continuous electrophoresis.

By this method the serum to be fractionated is applied to the top edge of a hanging sheet of filter paper down which buffered electrolyte flows, and along the vertical edges of which electrodes are applied which enable a potential difference to be applied across the sheet. Thus in travelling down the paper with the flowing electrolyte, the ionized components of the serum migrate towards their appropriate electrodes, at rates which are a function of their electrophoretic mobility. As equilibrium is established, the slow-moving anions form bands across the sheet, and can be collected by arranging tubes along serrations cut in the bottom edge.

Method

The continuous electrophoresis apparatus used was made up after the design of Holdsworth (1955). The flowing electrolyte was a barbitone buffer *p*H 8.6 made by dissolving 1.84 g. of barbitone and 10.3 g. of sodium barbitone to 1 litre of aqueous solution. The apparatus accommodated paper sheets 17 in. (43 cm.) horizontal by 20½ in. (52 cm.) vertical, and in use a potential difference of 1,000 v. was applied to platinum electrodes in contact with the vertical edges of the wet paper. The serum was diluted 1:1 with buffer and applied, so diluted, at the rate of 0.5–1 ml. per hour by means of an automatic slow-motion drive to the plunger of an all-glass syringe. Adequate separation was achieved in 24–48 hours, during which time the serum flow rate was adjusted to apply a total volume of 10–15 ml. The buffer flowing from the serrated bottom edge of the sheet carried the separated fractions into collecting tubes. At the end of the run the positions of the separated fractions across the sheet were determined by immersing the sheet in a dye-bath of the wool dye lissamine green S.F. ; after rinsing in 1% aqueous acetic acid the serum protein components showed as green bands.

Portions of fluid from each of the collecting tubes were then separately tested in the Schultz–Dale bath against the immune uterus. It was soon found that the diethylbarbituric acid of the buffer inhibited contractions and it was found necessary to dialyse each sample in "Visking cellophane" membranes against running water for 12 hours before testing.

In other experiments to achieve partial breakdown of serum proteins it was found that hydrolysis of serum for three hours with 3 vols. of 2 N HCl resulted in complete loss of activity, and trials with globulins precipitated by dialysis of the serum showed no activity in these fractions.

Results

Electrophoretic separation was carried out as described on five sera, and in all cases it was found that the active material appeared in the two or three collecting tubes immediately preceding the albumin. It was thought that this indicated a protein or polypeptide of low molecular weight.

Hydrolysis of the active material with 2 N HCl for two hours at 100° C. and subsequent paper chromatography of the hydrolysate, using the phenol–water and collidine–lutidine–water systems, gave large spots due to arginine and to the nephrosis peptide.

This finding of a peptide associated with nephrotic urine suggested an examination by paper chromatography of the urine of carcinoma patients. In each case samples of 150 µl. of urine were examined with the results shown in the Table. The urine of one patient with leiomyosarcoma also showed a spot in the position of nephrosis peptide.

Site of Carcinoma	No. of Patients		
	Tested	Showing Nephrosis Peptide	Not Showing Nephrosis Peptide
Breast	5	3	2
Colon and rectum	4	4	0
Lung	6	5	1
Prostate	3	2	1
Thyroid	2	2	0
Oesophagus	1	1	0
Total	21	17	4

Discussion

The demonstration of a polypeptide showing immunological specificity in the serum of patients with carcinoma is of interest in the light of the findings of Winzler (1953) that there is an increase in polypeptides in the serum in carcinoma, and specifically of mucopolypeptide. A quantitative rise in mucoprotein in the serum is a feature of pneumonia, tuberculosis, rheumatic fever, and other diseases (Winzler and Smyth, 1948), but it appears from the above findings that the serum in carcinoma contains a specific polypeptide, although much further study is necessary to prove this and to gain further information about its nature. It had been hoped that isolation of the active material from serum would facilitate the production of a superspecific antigen for sensitizing guinea-pigs in the Schultz–Dale test, but if the active substance is a polypeptide it presumably acts as a hapten and is therefore incapable of producing sensitization by itself.

The finding of a high proportion of arginine in the acid hydrolysate of the active fraction is in keeping with the observations of Toennies (1947), who quotes Schenk (1934), Rosedale (1928), Zbarskii *et al.* (1944), Annau and Gözsy (1934), and Klein and Ziese (1932) to the effect that tumour tissue has consistently a higher proportion of arginine than normal tissue, and indeed no abnormality of amino-acid composition is more regularly found.

In the same way the occurrence of the nephrosis peptide in the active serum fraction is striking in view of the number of false-positive carcinoma tests which have previously been shown to be found in patients with nephrosis (Burrows, 1958). Such a finding could be interpreted in several ways.

1. The polypeptide found in patients with carcinoma and the nephrosis peptide of Dent are identical, and are responsible for the positive reaction in the Schultz–Dale test. This is unlikely in view of the failure to detect the nephrosis peptide in some cases of carcinoma which give a positive Schultz–Dale test and from the absence of a positive Schultz–Dale test in many cases of nephrosis in which there is high excretion of the peptide.

2. The nephrosis peptide and the polypeptide in carcinoma may be identical but not specifically related to either disease process nor responsible for the Schultz–Dale test. This is supported by the theory of Arneil and Wilson (1953), who suggested that the nephrosis peptide is antidiuretic hormone which is for some reason raised in nephrosis. Paper chromatography of 50 µl. of a commercial "pitressin tannate" showed a well-marked spot in the position of nephrosis peptide which lends support to this view. Further, it has been shown that, in addition to an increased blood volume in patients with cancer, even the unaffected tissues of tumour-bearing animals contain a significantly higher water content than the corresponding tissues of normal animals (Robertson and Kahler, 1942). Since the body fluid volume is largely regulated by the release of antidiuretic hormone it might be reasonable on this evidence to expect a higher circulating level of antidiuretic hormone in patients with carcinoma.

To investigate this question it was decided to study patients with advanced mammary carcinoma on whom hypophysectomy had been carried out and who had thus had their source of antidiuretic hormone removed. Two of these patients were excreting more than 5 l. of urine in 24 hours, so that there was no evidence of hypothalamic antidiuretic hormone. Paper chromatography of the urine from these cases showed well-defined spots due to nephrosis peptide, in amounts comparable to those in untreated carcinoma. It is thus suggested that the nephrosis peptide is not identical with antidiuretic hormone.

3. The nephrosis peptide may be a breakdown product of a larger structure, produced in carcinoma from the tumour itself, and in nephrosis from the accelerated protein catabolism known to occur. This assumes, with C. E. Dent (1957, personal communication), that the nephrosis peptide is a group of polypeptides, and could be produced by a number of breakdown processes. The false-positive Schultz–Dale tests produced in some cases of nephrosis would then be the result of antigenic similarity between the group of polypeptides produced in this condition and the group produced in carcinoma. In the light of the above findings it is thought that this is the most likely explanation of the results.

Summary

A polypeptide has been found in the serum of patients with carcinoma and not in the serum of normal persons or of patients with other diseases.

The substance shows immunological features similar to carcinoma tissue and underlines the difference between normal and carcinomatous tissue.

This polypeptide is the active substance in the Schultz–Dale test for carcinoma.

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THE "UNEXPLAINED" HIGH ERYTHROCYTE SEDIMENTATION RATE

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Routine estimation of the erythrocyte sedimentation rate (E.S.R.) in new patients attending a rheumatism clinic sometimes reveals a value inexplicable in terms of the clinical diagnosis—for example, when the affliction is thought to be of a non-inflammatory nature, such as degenerative joint disease or "psychogenic rheumatism." Such cases often remain diagnostic problems, and we have therefore reviewed all these cases seen over a period of 3½ years. It seems to us important to document them, since medical literature in general neglects such patients (although they occur in every clinic) and tends to record only those who can be fitted into well-defined nosological categories.

Method and Material

Westergren's (1926) method was employed, and due precautions were taken with regard to contamination of the sample with skin-sterilizing alcohol (Sykes, 1948), to delay before setting-up of the sedimentation tube, to its verticality and cleanliness (Ham and Curtis, 1938), and to the room temperature (Romanus, 1944).

From February, 1952, until September, 1955, 51 out of approximately 900 estimations on new patients were found to be above 20 mm. per hour for no good clinical reason. Of these 51 cases 45 were re-examined and the E.S.R. was estimated again within one month of their first visit. In 14 it had returned to normal, so these patients were classified as having a transient rise in their E.S.R. and are designated group II. The E.S.R. in the remaining 31 patients remained abnormally high, and these are referred to as group I.

Another re-examination of these group I patients was made in the out-patient department, looking particularly for evidence of tissue destruction or inflammation. No abnormality which could account for the high E.S.R. was found. A chest *x*-ray examination, a full blood count, and a second urine examination were then done, with negative results. The initial diagnoses are shown in Table I.

TABLE I.—*Initial Diagnosis in 45 Cases with Unexplained High E.S.R.*

	Group I	Group II
Degenerative joint disease	18	4
Arthralgia	4	1
Cervical spondylosis	2	1
Phlebothrombosis	2	1
Psychogenic rheumatism	1	2
Oedema of an extremity	1	1
Postural backache	1	1
Osteoporosis of spine	1	0
Osteochondritis	1	0
Iritis and arthralgia	0	1
Acroparaesthesiae	0	1
Prolapsed intervertebral disk	0	1
Total	31	14

Since a raised E.S.R. may be the only sign of serious disease such as carcinoma or myelomatosis, further investigations, including for most patients electrophoresis of the serum for protein pattern, differential agglutination titre (D.A.T., Rose-Waaler), C-reactive protein, fibrinogen estimation, L.E. cells, antistreptolysin titre, and serum uric acid, were made. According to the results of these, other investigations were then instituted, including barium meal, barium enema, intravenous pyelography, and electrocardiography. In all cases with joint symptoms a careful review of the *x*-ray films was undertaken, and in certain cases biopsy of the bone marrow or synovial membrane was made, and for these the patient was admitted to hospital.

Results

In only a small number of cases was it possible to establish the cause of the raised E.S.R. after preliminary investigations, but the subsequent follow-up has allowed us to make a diagnosis in 20 out of the 31 in group I and in 7 out of 14 in group II cases (Table II). It can be seen that

TABLE II.—*Final Conclusion on the Cause of Unexplained High E.S.R.*

	Group I	Group II
Rheumatoid arthritis	8 (+ D.A.T. 4)	2 (+ D.A.T. 1)
Probable rheumatoid arthritis	6 (+ D.A.T. 1)	1
Ankylosing spondylitis	0	1
Phlebothrombosis	2	1
Carcinoma of bronchus	1	0
Tuberculosis of knee	1	0
Myelomatosis	1	0
Presence of cold agglutinins	1	0
Diverticulitis	0	1
Chronic bronchitis	0	1
Unexplained: Persisting more than 1 year	5	0
Unexplained: Settled in 1 year	6	7
Total	31	14

in a large number of patients who were thought at first to have solely degenerative joint disease a final diagnosis of rheumatoid arthritis was made.

A final diagnosis of rheumatoid arthritis was made in patients with polyarthritis (1) with a positive D.A.T., or (2) with erosions on *x*-ray films, or (3) with low viscosity high-protein-containing synovial fluid without infection. The final diagnosis of probable rheumatoid arthritis was made in patients with neither a positive D.A.T. nor *x*-ray erosion, but in whom pain, swelling, and limitation were present in multiple joints over a period of at least six months, without evidence of other conditions such as Reiter's syndrome, psoriasis, rheumatic fever, tuberculosis, lupus erythematosus, etc.

Case Histories to Illustrate Particular Points

Case 1 (Group I): Initial Diagnosis—Oedema, Not Yet Diagnosed; Final Conclusion—Rheumatoid Arthritis.—A 50-year-old woman was first seen in 1953, when she gave a two-year history of bouts of arthralgia persisting for three to four days every few weeks, and now complaining of intermittent swelling of the dorsum of both feet for six weeks. Apart from pitting oedema of the dorsum of the feet there were no abnormal physical signs, *x*-ray films were normal, and the Rose test (Rose *et al.*, 1948) was negative, but the E.S.R. was persistently raised about 30 mm. in one hour. The oedema settled, but she continued to have arthralgia. Two years later she developed swelling of the joints, initially palindromic but later persistent, and associated with severe pain and limitation of movement in the shoulder-, wrist-, finger-, knee-, ankle-, and toe-joints; the Rose test was now positive, and erosions have shown on the *x*-ray pictures of the hands and feet.

Case 2 (Group II): Initial Diagnosis—Oedema ? Due to Lymphatic Obstruction; Final Conclusion — Rheumatoid Arthritis.—A 66-year-old woman presented with oedema of the dorsum of the left hand which was thought to be due to lymphatic obstruction secondary to a radical mastectomy. No other abnormal signs were found, but the E.S.R. was 42 mm. in one hour. Over the next two and a half years she had occasional swelling of the left hand, but the E.S.R. returned to normal. She then developed pain and stiffness in both wrists followed by soft-tissue swelling. Other joints have become involved, the E.S.R. has risen to 60 mm. in one hour, and numerous erosions show on the *x*-ray pictures.

Case 3: Initial Diagnosis—Degenerative Joint Disease; Final Conclusion—Rheumatoid Arthritis.—A 77-year-old man presented with pain and stiffness of the legs, worse after rest and improved by walking, for the preceding 12 months. There was minimal

limitation of full knee flexion and no other abnormal signs. The E.S.R. varied between 30 and 35 mm. in one hour, and C-reactive protein was persistently present in the blood. The D.A.T. was positive 1:32. The *x*-ray films showed only mild degenerative changes. With analgesics and physiotherapy he has shown slight improvement over the year. The E.S.R. has remained raised, but he has not developed any other evidence of disease. In this case the most likely diagnosis was thought to be "anarthritic" rheumatoid disease.

The diagnosis of mono-articular arthritis at any age may be difficult. In group I there were two patients, both middle-aged (56 and 63) and both known to have had degenerative joint disease for some time, in whom the development of an effusion was thought to be a traumatic synovitis. In view of the rise in E.S.R. further investigations were undertaken, although the *x*-ray films showed only degenerative joint disease. In one the synovial fluid showed a high-protein content with a low viscosity, while the D.A.T. was positive, and the subsequent course has been that of rheumatoid arthritis. The synovial fluid in the other patient was compatible with degenerative joint disease, but, as his symptoms persisted despite physiotherapy and the E.S.R. remained high, he was persuaded to have a synovial biopsy performed. Histologically this case was of tuberculous aetiology, later confirmed bacteriologically.

Difficulty in Establishing Cause of Raised E.S.R.

Case 4: Initial Diagnosis—Osteoarthritis of the Knees; Final Conclusion—Multiple Myelomatosis, Osteoarthritis of Knees, Chronic Bronchitis.—A 70-year-old woman was first seen in February, 1954, complaining of pain and swelling of both knees of five years' duration. Asthmatic bronchitis had rendered her dyspnoeic on exertion for many years. She was very obese and had poor movement of her chest with widespread rhonchi. Both knees showed degenerative joint disease. The E.S.R. was 30 mm. in one hour; haemoglobin, 12 g. per 100 ml. The urine showed albuminuria. Blood urea was 41 mg. per 100 ml. *X*-ray films showed degenerative joint disease in the knees and a large left ventricle with considerable unfolding of the aorta. She was treated as an out-patient for degenerative joint disease with analgesics and physiotherapy, and was given dietary advice. Because of increasing dyspnoea on exertion and at night, as well as persistent pains in the legs, she was admitted in June, 1954, when she had albuminuria; E.S.R., 83 mm. in one hour; D.A.T., 1:2; total serum proteins, 8.5 g.% (albumin 4.3 g., globulin 4.2 g.); blood cholesterol, 248 mg. per 100 ml.; haemoglobin, 14 g. per 100 ml.; W.B.C., 3,600 c.mm. In view of the high E.S.R. and abnormal proteins it was suggested that her joint symptoms might be due to rheumatoid arthritis. She was treated with physiotherapy and analgesics with good effect, but the E.S.R. rose to 110 mm. in one hour, the haemoglobin fell to 8.7 g., and the electrophoretic pattern of the proteins became more abnormal and suggestive of myeloma. A sternal marrow examination was performed which showed 60% myeloma cells. There was no evidence of Bence Jones protein in the urine and no radiographic bone changes. The E.S.R. has continued to rise and haemoglobin to remain low, but in spite of generalized limb pain no radiographic abnormality has been detected.

Rise in E.S.R. in Relation to Disease

When this study was first begun the possibility that a raised E.S.R. could result from malignant disease as yet asymptomatic was very much to the fore in our minds. However, only one of our cases has so far proved to have a neoplasm, and in this case the diagnosis was not made until necropsy.

Case 5: Initial Diagnosis—Degenerative Joint Disease of Lumbar Spine; Final Conclusion—Carcinoma of Bronchus With Secondary Deposit.—A 63-year-old woman was seen in 1952 with a left-sided sciatica of two weeks' duration. In 1945, because of cough and haemoptysis, she had had a chest *x*-ray examination which revealed a shadow at the right apex. Investigations for neoplasm, including bronchoscopy, were negative. At the time we saw her her chest symptoms and *x*-ray picture were unchanged. All other investigations were negative and she improved on bed rest. Nine months later she developed bronchopneumonia and was admitted elsewhere, where she died.

In a few cases the cause of the raised E.S.R. bore no relationship to the disease process which brought the patient to our clinic.

Case 6: Initial Diagnosis—Cervical Spondylosis; Final Conclusion—Cervical Spondylosis, Cold Agglutinins.—A 42-year-old woman complained of pain and paraesthesiae in the left shoulder and arm. She showed marked limitation of movement of the cervical spine, and *x*-ray examination confirmed the presence of osteoarthritis in the cervical spine, involving the fifth and sixth vertebrae. The E.S.R. was raised to 100 mm. in one hour. Full investigations were instituted and a high titre of cold agglutinins discovered, 1:8,102 (2—5° C.), 1:128 (20° C.), 0 (37° C.). It was felt these probably accounted for the E.S.R. abnormality.

Cases in Which No Cause for High E.S.R. was Found

If we consider the patients in whom no cause for the high E.S.R. could be found, these fall into two types: those in whom the rate fell to normal with remission of their symptoms but in whom no diagnosis was made, and those in whom it persisted at a high level. The following is an example of the first type:

Case 7: Initial Diagnosis—Arthralgia; Final Conclusion—Unexplained High E.S.R. Which Settled.—A 25-year-old man was seen in October, 1953, with a history of a sore throat one year previously, followed by fever and general arthralgia. He had been treated with various antibiotics, with no apparent response, subsequently improved, but then began to have bouts of intermittent fever and arthralgia lasting two to three days at a time. There were no abnormal physical signs apart from right axillary and bilateral epitrochlear lymphadenopathy. The E.S.R. was 28 mm. in one hour, and all other investigations, including L.E. cells, blood culture with CO_2 preparation, Coombs test, *Brucella abortus* agglutinations, D.A.T., plasma proteins, liver biopsy, E.C.G., *x*-ray examination of the joints and chest, and barium meal, were negative. While in hospital he continued to have pyrexial episodes spiking to 102° F. (38.9° C.), lasting for two to three days and remitting spontaneously; in some of these acute arthritis of the mid-tarsal joints developed, and on one occasion there was a small effusion into the right knee-joint. Occasionally he also had purpuric spots on the chest and limbs, although bleeding- and clotting-times and platelet counts were never abnormal. Salicylates caused symptomatic improvement; he gradually improved and the E.S.R. slowly returned to normal over a few months. He has remained well during the past 18 months with only occasional arthralgia.

It is of course possible that he had a mild rheumatoid arthritis which cleared completely, or Schönlein–Henoch purpura, or rheumatic fever, but these diagnoses could not be substantiated.

There have been some patients in whom the raised E.S.R. has persisted, whose general health has remained good, and in whom the E.S.R. was not apparently related to the patient's symptoms.

Case 8: Initial Diagnosis—Degenerative Joint Disease of the Knees; Final Conclusion—No Cause for High E.S.R., Degenerative Joint Disease, Knees.—A 75-year-old woman was seen in August, 1954, complaining of pain in both knees, particularly the right, for 20 years, which was getting worse. On examination, apart from obesity, she showed only degenerative joint disease involving both knees. The E.S.R. was 23 mm. in one hour and *x*-ray examination confirmed the presence of degenerative joint disease. She was treated by weight reduction, analgesics, and physiotherapy with an excellent response, but in the subsequent two years her E.S.R. has remained between 30 and 35 mm. in one hour; the D.A.T., 1:2; protein, 6.8 g.% (albumin 3.6 g., globulins 3.2 g.); haemoglobin, 13.7 g. per 100 ml.; L.E. cells negative; and no other changes have shown on *x*-ray films.

In other cases the E.S.R. appeared to be related to the disease process, but a diagnosis could not be established.

Case 9: Initial Diagnosis—Psychogenic Rheumatism; Final Conclusion—Not Yet Diagnosed, Persistently Raised E.S.R.—A 47-year-old man noticed in 1954 the sudden onset of difficulty in walking because of stiffness and tightness of the legs associated with some weakness. At this time he had reddish-blue discoloration of toes and blotching of the dorsa of both feet, but no true claudication and no superficial phlebitis. On three occasions he had a rash on his legs, which when seen in the last attack was of a macular type. In addition he complained of general malaise, tiredness, headache, but had not lost weight, nor had he any history of fever. On examination he was very introspective, but no abnormal physical signs were found, apart from the remains of a rash. His E.S.R. varied between 100 and 118 mm. in one

hour; haemoglobin, 12.9 g. per 100 ml.; W.B.C., 6,000 (normal differential); urine normal, no albumin or Bence Jones protein, no L.E. cells; W.R. negative; A.S.T., 75; D.A.T., 1:2; total protein, 7.3 g.% (albumin 4.1 g., globulin 3.2 g.); protein electrophoresis normal; no cryoglobulins or other abnormal protein, apart from fibrinogen, which was 616 mg. per 100 ml.; acid and alkaline phosphatase, normal; blood urea, normal; *x*-ray film of lumbar spine normal; *x*-ray film of the sinuses showed some opacity of the right antrum. He has been reviewed by Dr. Edwin Clark, who could find no neurological abnormality, and by Mr. Peter Martin, who could find no abnormality in the peripheral vessels. Over the past two years his symptoms have gradually subsided with reassurance and analgesics. The E.S.R. remains between 60 and 80 mm. in one hour, and he still has a high fibrinogen content of the blood.

Here one of the rarer collagen disorders, such as polyarteritis nodosa, was considered but not established.

Discussion

Although the E.S.R. is higher in women than in men and shows some day-to-day variation, particularly in women (Greisheimer, 1927) and quite apart from menstruation (Benson and Rogers, 1941) and pregnancy (Hamilton, 1953), in normal adults it does not exceed the value of 20 mm. in one hour, which we have taken as our upper limit of normal. As age increases, the sex difference is less obvious and the normal level tends to rise, showing a wider range (Reinbourne, 1952).

In group I 15 of our patients were over 60 years, 10 between 50 and 60, and six under 50. However, of those in whom we were unable to find an adequate explanation for the rise in E.S.R. only three were over 60, five being between 50 and 60, and three under 50. It does not seem likely to us that in the two cases (Nos. 13 and 17) of the oldest age group, who have remained in good health and have now been followed for three and two years respectively with the E.S.R. remaining between 20 and 30 mm. in one hour, the raised value is due solely to their age and random variation, since in a third similar case the E.S.R. settled under observation in five months. That it is important not to accept age as the reason for an E.S.R. between 20 and 30 until full investigations have been carried out is shown by other patients with a similar initial reading who have later developed obvious rheumatoid arthritis or been found to be suffering from such diseases as tuberculosis of the knee.

Out of 31 cases in group I a disease process was diagnosed in 20, although in some it did not become obvious for a period of time. These results are similar to those of Cutler (1932), although the actual final diagnosis differed from his, since his series showed a high incidence of chest diseases. Similarly, our results should not be strictly compared with those of Liljestrand (Liljestrand and Olhagen, 1955; Olhagen and Liljestrand, 1955), since our cases were selected by referral to a rheumatology clinic, whereas his came from a general medical clinic. However, we agree with him that carcinoma as a cause of this high E.S.R. is rare. In his series of 37 cases with a raised E.S.R. of obscure cause, no final explanation could be given in 21 cases, and these were all women. In our similar group of 11 cases, 8 were women, and the prognosis does not seem at this distance to be bad.

The high incidence of rheumatoid arthritis in patients of advancing years and the difficulty in establishing its diagnosis are of particular interest. Clinically, a fairly confident diagnosis was made in 14 of the patients, though only eight fulfilled the criteria described earlier. This problem has been discussed by Bagratuni (1956), who described what he calls "anarthritic rheumatoid disease." The entity, described sometimes as the fibrositic prodromal phase of rheumatoid arthritis, is well known (Ropes and Bauer, 1945); but whereas in his cases there was little evidence to suggest joint involvement, in all except one of ours there was ultimately definite evidence of arthritis. The value of a rise in E.S.R. in differentiating early arthritis from fibrositic pains has also been stressed by Slocumb (1936), and can be confirmed by us in cases not included in this series.

Summary

An unexplained rise of the sedimentation rate above 20 mm. in one hour was found in 51 new patients out of approximately 900 attending a rheumatology clinic over a period of 3½ years.

Thirty-one of these remained high over one month, and eight of them have developed typical rheumatoid arthritis, while six are probably suffering from this disorder. In eleven others no cause for the raised E.S.R. could be found, and their general health has remained good. In five it returned to normal within one year, while in six it has remained high.

The presence of a high E.S.R. should lead to a careful assessment and investigation of the patient, but, particularly in older people, it is not necessarily associated with a bad prognosis.

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THERAPEUTIC TRIAL OF AZACYCLONOL

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Azacyclonol ("frenquel") has been the subject of pharmacological study in America since 1954. Chemically it is related to pipradol hydrochloride ("meratran"), which is alpha-(2-piperidyl) benzhydrol hydrochloride, while azacyclonol is the gamma isomer, alpha-(4-piperidyl) benzhydrol hydrochloride. Azacyclonol has been shown to protect subjects against the experimental psychosis induced by lysergic acid diethylamide (Fabing, 1955). The central effect appears to differ from that of reserpine and chlorpromazine, which act on the mesodiencephalic activating system. Azacyclonol again differs in its effects from pipradrol hydrochloride, which is believed to be a central stimulant without concomitant autonomic effects (Rinaldi, Rudy, and Himwich, 1955). Favourable clinical responses to azacyclonol in various psychotic states have been reported (Fabing and Hawkins, 1955; Cohen and Parlour, 1956; Browne, 1956). The best responses were obtained in toxic hallucinatory states (Proctor and Odland, 1956), whereas the results in schizophrenia have been somewhat variable. This paper presents the results of treatment with azacyclonol in 56 patients with schizophrenia and two patients with alcoholic hallucinatory states.

Controlled Trial

Forty patients (20 female and 20 male) were the subjects of a controlled trial. The mean age of the women was 51, with a range of 28–75 years. The mean age of the men was 38, with a range of 18–63 years. For the whole group the length of stay in hospital ranged from 6 months to 27 years, the mean being 10 years. The diagnosis in each case was schizophrenia (hebephrenia 20, paranoid schizophrenia 19, catatonic schizophrenia 1). The only criteria for admission to the trial were that the diagnosis was schizophrenia and that the patient appeared to be subject to hallucinatory experience. Thirty patients were able to discuss these experiences at interview. We decided that it would be unreasonable to withdraw any drugs the patients were already receiving, provided that there had been no change in their mental condition attributable to these drugs in the four weeks prior to the onset of the trial. In fact, 17 patients were receiving reserpine and 6 were receiving chlorpromazine. These drugs were continued unchanged during the course of the trial. On the other hand, we decided that if a patient's clinical condition indicated E.C.T., then that patient would have to be withdrawn from the trial. One man was withdrawn for this reason after three days. Two women were withdrawn after five days, as they refused to take the tablets. These three patients were replaced, the replacements being "scored" as if they had begun the trial on the proper date.

Allocation to Groups.—With the use of random numbers (taken from Bradford Hill's *Principles of Medical Statistics*) the patients were allocated to four groups of 10. The pharmacist had meanwhile made up the azacyclonol (20 mg.) and placebo tablets into bottles labelled A and B. Group 1 had five weeks on A, then five weeks on B. Group 2 went through the reverse sequence. Group 3 had tablet A and Group 4 had tablet B for the whole period of 10 weeks. The dose was 1 tablet three times a day. The nature of tablets A and B was known only to the pharmacist until the trial was completed.

Method of Assessment.—All the patients were interviewed before the trial. Further interviews were held at 3, 5, 7, and 10 weeks, each observer seeing the same patients throughout. At each interview information regarding hallucinations, delusions, and range of activity was recorded on a prepared card. In addition a clinical rating—that is, improved, no change, or worse—was entered on the card. During the period of the trial (10 weeks) white blood cell counts were made at fortnightly intervals on each patient.

Toxicity Study

Four patients were studied outside the controlled trial. These patients were kept in bed and were given azacyclonol, 60 mg. daily. Temperature, pulse, and blood pressure (supine position, mean of two readings) were recorded twice daily. Liver-function tests, estimation of blood urea nitrogen, and W.B.C. counts were performed on the day before and on the second and ninth days of the trial. Fluid intake and output were measured over 24-hour periods before the trial and during the sixth day and night. The patients were examined for evidence of skin rashes before and on the ninth day of the trial.

Clinical Trial

Apart from the controlled trial, 18 patients have been treated with azacyclonol over periods ranging from four weeks to three months. The dosage has varied from 60 to 180 mg. daily. The mean age of this group is 30, with a range of 18 to 42 years. The diagnoses were schizophrenia (16 patients) and alcoholic hallucinatory states (2 patients). The length of stay in hospital ranged from one day to 10 years, the mean being 18 months.

Results of Controlled Trial

In accordance with the method described above it was possible to compare the changes in clinical rating during 30 "azacyclonol periods" and 30 "placebo periods" in the 40 patients under study. The results are shown in Table I.

TABLE I.—*Controlled Trial* (40 *Patients*)

Treatment	No. of Patients	No Change	Improved	Worse	Total
Azacyclonol ..	30	19 (63·4%)	10 (33·3%)	1 (3·3%)	30
Placebo ..	30	15 (50%)	14 (47·7%)	1 (3·3%)	30
Total ..	60	34 (56·7%)	24 (40%)	2 (3·3%)	60

$\chi^2 = 0{\cdot}556$. $P < 0{\cdot}5 > 0{\cdot}2$.

Two points of interest emerge from these rather surprising results. Firstly, a comparison of the results in patients receiving other drugs with those receiving azacyclonol alone. There were 11 patients who received azacyclonol alone, four of these showing improvement. Of the 19 who received other drugs in addition to azacyclonol, six showed improvement. The difference is not significant. Secondly, in the male patients there were some obvious changes in activity during the trial—that is, activity as exemplified in the interview situation; for instance, the patients were more talkative and restless. In fact, one of them was rated as worse on account of more obvious disturbance in thinking and perception. The changes in the 20 male patients are shown in Table II.

TABLE II.—*Controlled Trial* (20 *Male Patients*)

Treatment	No. of Patients	Activity Rating		
		More Active	No Change	Total
Azacyclonol	15	5	10	15
Placebo	15	0	15	15
Total ..	30	5	25	30

$\chi^2 = 2$. $P < 0{\cdot}2 > 0{\cdot}1$

As regards alteration in hallucinatory experience, evidence is available about 30 patients (involving 47 periods of observation) who were willing and able to discuss their hallucinatory experiences at interview. Every patient had auditory hallucinations, but three patients had visual hallucinations in addition. The results are shown in Table III. Two patients claimed that their visual hallucinations stopped entirely; as regards the auditory hallucinations, our impression was that, although there was a diminution in intensity and frequency in some patients, in none of the patients did the experience cease entirely.

TABLE III.—*Controlled Trial* (30 *Patients*)

Treatment	Changes in Hallucinations		
	No Change	Improved	Total
Azacyclonol	19	5	24
Placebo	20	3	23
Total ..	39	8	47

Results of Toxicity Studies

The W.B.C. counts made at fortnightly intervals during the controlled trial revealed no significant alteration during either the azacyclonol or the placebo periods. There was no observed alteration in temperature, pulse, blood pressure,

TABLE IV.—*Fluid Balance and Blood Urea Nitrogen Before and During Treatment with Azacyclonol*

Patient	Pre-trial				Azacyclonol			
	Intake (oz.)	Day Urine (oz.)	Night Urine (oz.)	B.U.N. (mg./100 ml.)	Intake (oz.)	Day Urine	Night Urine	B.U.N. (mg./100 ml.)
M. McC.	44	53 (1012)	22 (1024)	11·6	54	51 (1014)	27 (1022)	16·2
W. S. ..	40	31 (1012)	24 (1014)	24·5	64	46 (—)	59 (1014)	55·0
J. McG.	42	29 (1018)	16 (1022)	16·2	48	54 (—)	14 (1024)	9·3
J. C. ..	52	16 (1022)	16 (1024)	12·9	48	36 (—)	19 (1020)	10·6

The figures in parentheses refer to the specific gravity of the urine samples.

W.B.C. counts, or liver-function tests in the four patients subjected to detailed study. Two patients showed an increase in blood urea nitrogen; in both cases there was an associated alteration in fluid balance with a tendency to an increased volume of night urine (see Table IV). None of these patients showed any abnormal urinary constituents at this time. One patient (W. S.) had previously been suspected of having renal damage, but investigations had been negative. Subsequent to this trial he was found to have evidence of renal changes compatible with a diagnosis of chronic nephritis, although he was at the time symptom-free.

Results of Clinical Trial

These patients were seen by one of us (A. D. F.) before treatment was begun, and thereafter at intervals of three weeks. The changes in "clinical rating" and in hallucinatory experience are shown in Table V.

TABLE V.—*Clinical Trial: Changes in Clinical Rating and Hallucinations (18 Patients)*

	No Change	Improved	Worse	Total
Clinical rating	5	13	—	18
Hallucinations	10	8	—	18
Total ..	15	21	—	36

It should be emphasized that in four patients the hallucinatory experience stopped completely. Two of these later received E.C.T., but in each case there had been a reduction in hallucinatory experience before the E.C.T. was begun. Three patients were on reserpine and three on chlorpromazine when the azacyclonol was introduced. These drugs were continued as in the controlled trial. These patients did rather worse than the group as a whole—that is, only two out of the six improved. Of the 13 patients who improved on azacyclonol, four have since been discharged and two have left hospital for a period of leave. We are maintaining these patients on smaller doses of azacyclonol (40–60 mg. daily).

Illustrative Cases

Brief case histories of two patients who have left hospital are reported.

Case 1 (Diagnosis: Alcoholic Hallucinosis).—A 41-year-old man, who gave a past history of alcoholism, had been admitted to hospital on three previous occasions, but had never before experienced hallucinations. The family history was negative. Three weeks before admission he began drinking heavily, but stopped suddenly after four days. Three days later he began to have auditory and visual hallucinations, and these persisted until his admission. Physical examination on admission revealed no evidence of hepatic enlargement or of peripheral neuritis. Mentally he was tense, suspicious, and intensely hallucinated. The auditory hallucinations were heard as the voices of friends and of the medical staff. He spent most of his time answering these "voices." He also saw, in the garden, visions of St. Francis of Assisi and McDonald of the Isles. There were no animal hallucinations. He was given parenteral vitamin B for one week and was then put on azacyclonol, 60 mg. t.d.s. His hallucinatory experience was greatly reduced by the end of three weeks. The visual hallucinations had stopped and the auditory hallucinations had diminished in intensity so that he now regarded them as "unreal," and was not obliged to answer them. Thereafter he was given E.C.T. (six treatments), and was symptom-free when he left hospital. When seen a month later he was found to be in good health.

Case 2 (Diagnosis: Schizophrenia).—A 19-year-old youth had a 10-day history, starting with a "blackout" at work. He then began to express strange ideas—for instance, that his drink at work was being tampered with. He became very argumentative; and on the night before admission he was very disturbed, walking up and down the street in his pyjamas. The patient's mother suffered from ideas of persecution and one brother was an epileptic. Physical examination on admission revealed no abnormality. An E.E.G. showed nothing conclusive, although there was some slow activity in the right temporal region. Mentally he was perplexed and restless. He was quizzical in manner and uncooperative in a humorous sort of way. He was auditorily hallucinated and felt he was being influenced by some agency outside himself. He was put on azacyclonol, 100 mg. t.d.s., but became very excited, and the drug was stopped after 48 hours. For a week he was treated with chlorpromazine (100 mg. t.d.s.); his behaviour became more controlled, but his hallucinations and feelings of being influenced persisted unchanged. Then the chlorpromazine was stopped and he was given azacyclonol, 60 mg. t.d.s. Three weeks later his hallucinations and feelings of influence had ceased. He was much more alert and no longer perplexed. He gave in his notice a week later and was discharged from hospital.

Discussion

This trial has served to emphasize some important factors involved in the evaluation of new drugs in psychiatry. Firstly, chronic schizophrenics improve as a result of the additional attention involved in any therapeutic trial. Secondly, psychiatric assessment when applied to minor degrees of change in mental state is not very precise, although probably more informative than any other techniques available. Many of the drugs at present used in chronic schizophrenia produce quite clear effects—for instance, the weight and behaviour changes of reserpine—and trials of such drugs are not really "blind." This trial was "blind": the nursing staff were unable to distinguish the active preparation from the placebo. Another point is that improvement in chronic schizophrenics treated with new drugs has usually implied greater conformity with the hospital regime. Such an effect is beneficial from the point of view of the hospital and of the patient, but is of little help in evaluating the effect of the drug on the disease process itself. Azacyclonol seems to have no sedative effect, and any improvement in behaviour appears to be secondary to the effects of the drug on the disturbances of thought and perception as seen in schizophrenia and some acute toxic psychoses. In fact, it is our impression that azacyclonol acts partly as a cerebral stimulant.

Feldman (1957), in a comparative study of various ataractic drugs, noted "turbulence" as a side-effect of treatment with azacyclonol in 10.7% of patients (the comparable figure for reserpine was 6.5%). "Turbulence" is here used, we understand, to describe the restless, active stage first reported by Barsa and Kline (1955) in regard to reserpine. In an attempt to check whether azacyclonol has any effect on normal people we gave 40 mg. (2 tablets) and placebo (2 tablets) on consecutive evenings to six normal volunteers (the drug order was randomized). Three reported no effects, two reported restlessness with azacyclonol, while one reported overactivity on both occasions, although more pronounced on the evening when azacyclonol was taken. These results, although quite inconclusive, are in line with the observations reported in the controlled trial.

Azacyclonol appears to have been the subject of the usual cycle of early enthusiasm and later criticism, although in this case there has been a fair degree of consistency among the reports in the literature. The earlier reports defined schizophrenia as the main indication, and reported good results in chronic as well as acute cases (Fabing and Hawkins, 1955; Rinaldi *et al.*, 1955). Later papers reported good results in acute schizophrenic reactions and in toxic hallucinatory states (Cohen and Parlour, 1956; Proctor and Odland, 1956). The most recent paper (Forster and Henderson, 1957) reports a trial in 18 chronic schizophrenics in which benefit was observed in only one patient. The dosage used in these various trials varied from 60 to 400 mg. daily.

The controlled trial reported here is open to several criticisms. The patients were all chronic and the dosage

was small (60 mg. daily). More important was an intrinsic defect in our method of assessment, which resulted in the apparent superiority of the placebo to the drug. We think that the explanation lies in the stimulant effect of the drug (equivalent to Feldman's observation of "turbulence"), which made the patient's mental disturbance more obvious in the interview situation. That this can also be true of reserpine we can confirm from personal experience. But, even allowing for these criticisms of our method, our results do suggest that azacyclonol is unlikely to be a very useful drug in the treatment of chronic schizophrenia.

The results of our clinical trial seem promising enough to warrant a more extensive trial of the drug in cases of acute schizophrenia and alcoholic hallucinosis. One difficulty in evaluating drug therapy of such acute cases is that a proportion remit spontaneously and no precise criteria are yet available for indicating which patients should have azacyclonol. Some later American papers—for example, Cohen and Parlour (1956)—suggested that azacyclonol had very little anti-hallucinatory effect. Our experience suggests that hallucinatory experience of recent onset, whether schizophrenic or toxic, is an indication for treatment with azacyclonol.

The only report of any toxic side-effect of azacyclonol is contained in the paper by Forster and Henderson (1957). They found elevation of the non-protein nitrogen in 11 out of 18 patients treated with azacyclonol. We have found similar changes in two patients. One of these was later shown to have signs indicative of chronic nephritis. However, the blood urea nitrogen did fall later to near normal levels when the dose of azacyclonol was reduced.

Summary

We have described a controlled trial of azacyclonol in 40 chronic schizophrenic patients. The results suggest that azacyclonol is not going to be of great value in the treatment of this type of patient.

We subsequently treated 18 patients (16 schizophrenics, 2 toxic hallucinatory states) with azacyclonol. The illness was of more recent onset in these patients than in those involved in the controlled trial: 13 patients improved and 6 have since left hospital.

Our clinical impression is that azacyclonol has a central stimulant action and that part of the poor result of the drug in the controlled trial was due to the masking effects of excitement and overactivity.

The only toxic effect observed was a rise of blood urea nitrogen in two patients out of a group of four who were subjected to detailed study. In one patient the elevation was not of significant degree, and in the other patient evidence of chronic nephritis was later established.

We thank Dr. T. A. Munro, physician-superintendent, for his advice and encouragement; Dr. D. Crombie and his staff for laboratory investigations; the nursing and secretarial staff for help in running the trial; and Mr. R. W. Richards, of Riker Laboratories, who kindly supplied us with frenquel and placebo tablets.

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Plans of the new building for the National Library of Medicine, Washington, provide for a five-story building with accommodation for 1,290,000 volumes (a little more than double the present number).

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH ORAL PHENOXYMETHYLPENICILLIN

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With the preparation of phenoxymethylpenicillin in 1947 by Behrens and his co-workers an important stable oral form of penicillin was introduced. Effective absorption and therapeutic blood levels have been reported by many observers (Wright *et al.*, 1955; Martin *et al.*, 1955; Rinsler and Cunliffe, 1956; Holborrow *et al.*, 1956). A number of diseases have been successfully treated with the drug, including pulmonary infections (Hart *et al.*, 1956), beta-haemolytic streptococcal infections (Breese and Disney, 1956), dental abscesses (Hermann, 1955), and gonorrhoeal urethritis (Marmell and Prigot, 1956; Love and Weir, 1956). In subacute bacterial endocarditis clinical experience with phenoxymethylpenicillin is more limited. A cautious approach is necessary in treating a condition which a relatively short time ago was associated with such a high mortality, and which responds so favourably in most cases to parenteral penicillin. This disease can be successfully treated by oral phenoxymethylpenicillin, however, as is shown by the two cases described, in one of which it was the sole form of antibiotic therapy.

Case 1

A female domestic worker aged 37 presented with a two-weeks history of headache, malaise, loss of energy, sore throat, joint pains, anorexia, vomiting, and fever. She gave a past history of acute rheumatic fever at the age of 24, when she was confined to bed for four months.

On examination she was pyrexial and had dental caries. Her fingers were clubbed. She had a sinus tachycardia, the characteristic murmurs of mitral stenosis and regurgitation, and moderate cardiomegaly, but no evidence of congestive cardiac failure. Her spleen was not palpable.

Investigations.—Haemoglobin, 8.1 g./100 ml.; leucocyte count, 12,000/c.mm.; E.S.R. (Westergren), 65 mm. in the first hour; microscopy of the urine showed red blood cells; *x*-ray examination of the chest showed a mitral cardiac configuration with increased pulmonary vascular markings; electrocardiogram showed notched P waves. Six blood cultures were negative, and this may have been due to a three-day course of sulphonamides just before admission to hospital, but the seventh yielded a growth of *Streptococcus viridans*.

Treatment was begun with intramuscular injections of crystalline penicillin, 500,000 units six-hourly, and this dose was gradually increased over two weeks to 3,000,000 units six-hourly in view of the persistence of pyrexia and elevation of the E.S.R.

Soon after parenteral therapy was started local pain and tenderness occurred at the injection sites, and was associated with progressively increasing bruising and oedema. The temperature remained high and a two-weeks course of streptomycin, 1 g. intramuscularly daily, was given, but with no effect on the raised temperature. At this time, because

of the severity of the local reactions to the injections, all parenteral therapy had to be stopped and oral penicillin started instead.

The potassium salt of phenoxymethylpenicillin was given, 399 mg. four-hourly by mouth, together with probenecid, 0.5 g. six-hourly. The potassium salt was given in preference to the free acid, as it produces higher peak concentrations (Colquhoun *et al.*, 1957). The temperature and

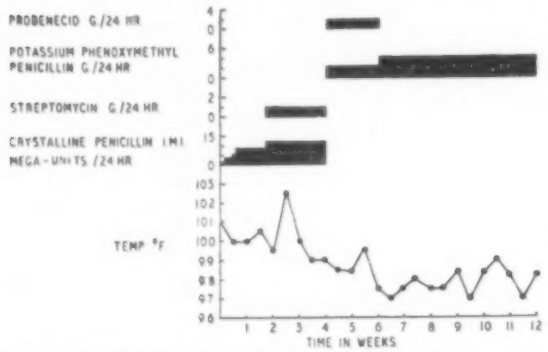

Chart showing antibiotic therapy and temperature in Case 1.

E.S.R. began to fall. Two weeks later the dose of potassium phenoxymethylpenicillin was increased to 1,064 mg. six-hourly, the probenecid being discontinued, and an uneventful convalescence ensued (see Chart). In spite of the very large doses of oral penicillin used, no gastro-intestinal or other toxic side-effects occurred. During the latter part of her convalescence dental treatment was successfully carried out. The patient was discharged after two months, and phenoxymethylpenicillin-free acid, 500 mg. four-hourly, was continued for the subsequent six months, during which the patient was kept under observation in the out-patient department.

Case 2

A housewife aged 46 was first seen complaining of a persistent attack of "bronchitis" for five months, associated with a productive cough, loss of energy, headaches, and shivering attacks. She had lost 12.7 kg. (28 lb.) in weight over the previous three months. She had rheumatic fever at the age of 19 years and was then in bed for three months.

On examination she was febrile, very emaciated, weighing only 28.6 kg. (63 lb.), and had marked pallor of her face and mucous membranes. Her fingers were clubbed and she had a typical Osler node in the pulp of her left middle finger. Her teeth were carious. She had a sinus tachycardia and a loud, blowing systolic murmur, maximal at the apex of the heart, with moderate cardiomegaly. There was no definite evidence of mitral stenosis, or any signs of congestive cardiac failure. Examination of her lungs indicated bilateral basal consolidation. The spleen was not palpable.

Investigations.—Haemoglobin, 12.7 g./100 ml.; leucocyte count, 12,000/c.mm. (76% polymorphonuclears); E.S.R. (Westergren), 70 mm. in the first hour; microscopy of the urine showed many red cells; *x*-ray examination of her chest showed bilateral basal shadowing consistent with partial collapse or consolidation; the electrocardiogram was normal; blood culture at the time of admission yielded a growth of *Strep. viridans*.

Treatment was begun with phenoxymethylpenicillin-free acid, 240 mg. two-hourly by mouth. Ten days later her temperature had become normal and her clinical condition was improving. The dose was then increased to 0.5 g. two-hourly, and two days later probenecid, 0.5 g. six-hourly, was added. Treatment was continued for a further six weeks, during which time rapid progress was made. The patient was discharged to continue phenoxymethylpenicillin, 240 mg. four-hourly. During the latter phase of convalescence, dental treatment was successfully carried out. Just before discharge from hospital the typical murmur of mitral stenosis became audible.

Serum Penicillin Levels

The estimation of serum penicillin levels was done by dilutions in phenol-red–glucose serum medium (May *et al.*, 1947).

In Case 1 the infecting *Strep. viridans* was sensitive to 0.06 unit of penicillin per ml. The Table shows the serum penicillin levels attained with parenteral penicillin and with different doses of oral phenoxymethylpenicillin with and without probenecid. It will be seen that the intramuscular dose of 3 mega units of crystalline penicillin produced a level of 64 units after one hour, which was more than adequate to deal with the invading streptococcus, but the temperature still remained elevated. Increasing doses of phenoxymethylpenicillin were given to assess whether the serum penicillin levels produced would be adequate therapeutically. With doses of 60 to 500 mg. the half-hour levels of 0.03 to 0.06 unit/ml. were barely adequate, although in every case the two-hour level was sufficient. With a 1-g. dose a half-hour level of 8 units/ml. was produced and a two-hour level of 2 units/ml. In view of these results it was considered advisable to maintain treatment with a dose of potassium phenoxymethylpenicillin of 1,064 mg., rather than with the initial dose of 399 mg. With the addition of probenecid, however, high blood levels of 16 units/ml. and 4 units/ml. at one and four hours respectively could be produced with this latter dose.

Serum Penicillin Levels

Type of Penicillin	Route	Dose	Dose of Probenecid	Serum Penicillin Levels (units/ml.)			
				½ hr.	1 hr.	2 hr.	4 hr.
Case 1							
Benzylpenicillin G	Intramuscularly	3 mega units	0	—	64	—	—
Phenoxymethylpenicillin potassium salt	Oral	399 mg.	2 g. daily	—	16	—	4
Phenoxymethylpenicillin-free acid	Oral	60 mg.	0	0·03	—	1·0	—
		120 ,,	0	0·06	—	2·0	—
		250 ,,	0	0·03	—	2·0	—
		500 ,,	0	0·06	—	2·0	—
		1 g.	0	8·0	—	2·0	—
Case 2							
Phenoxymethylpenicillin-free acid	Oral	60 mg.	0	0·03	—	0·5	—
		120 ,,	0	0·25	—	0·25	—
		240 ,,	0	0·5	1·0	0·5	—
		240 ,,	2 g. daily	—	1·5	—	—
		500 ,,	0	0·5	3·0	0·06	—
		500 ,,	2 g. daily	—	4·0	—	—
		1 g.	0	4·0	4·0	—	—

The Table shows the serum penicillin levels in Case 2 with increasing doses of phenoxymethylpenicillin-free acid and also the effect of adding probenecid in two instances. The infecting *Strep. viridans* was sensitive to 0.15 unit of penicillin per ml. The 60-mg. dose produced inadequate, and the 120-mg. dose produced barely adequate, blood levels. With larger doses the penicillin levels showed a progressive increase and a greater persistence, and the addition of probenecid raised the levels, from a one-hour level of 1 to 1.5 units/ml. with a 240-mg. dose and from 3 to 4 units/ml. with a 500-mg. dose. This patient, therefore, was given a maintenance dose of phenoxymethylpenicillin-free acid of 500 mg. two-hourly, together with probenecid 2 g. daily in view of the satisfactory blood levels produced by this regime.

It will be seen from the Table that effective therapeutic blood levels can be easily attained and maintained by adjustment of the dose of oral penicillin, given with the addition of probenecid if necessary, provided the sensitivity of the infecting organism to penicillin is high.

Discussion

There are reports of successful treatment of subacute bacterial endocarditis with phenoxymethylpenicillin. Quinn *et al.* (1956) describe four cases, in two of which a *Strep. viridans* infection was treated successfully with 7.2 g. daily for six weeks. In the third patient the infection was due to a species of *Neisseria*, and treatment comprised oral phenoxymethylpenicillin together with parenteral streptomycin and dihydrostreptomycin. The fourth case was less successful owing to a penicillin-resistant *Micrococcus pyogenes*. Martin *et al.* (1956) treated two cases successfully with doses of 12,000,000 units daily, supplemented with intramuscular streptomycin.

In the two cases reported here the use of oral penicillin was indicated by the difficulties associated with parenteral therapy. The first patient was beginning to respond favourably when intramuscular penicillin had to be abandoned owing to local reactions following the mechanical trauma of injections. The persistence of pyrexia in this patient, when the infecting organisms showed such a marked sensitivity to penicillin and the penicillin blood levels seemed quite adequate therapeutically, was thought to be due to the extensive tissue destruction associated with these local reactions. The rapid fall of temperature on withdrawal of injections tended to confirm this. In Case 2 parenteral therapy was not used at all, as the severe emaciation and loss of muscle tissue, especially of the buttocks, contraindicated a prolonged course of frequent injections. The high sensitivity of the infecting organism to penicillin and the therapeutic blood levels attainable with phenoxymethylpenicillin (see Table) were additional indications for this form of therapy. Though the use of phenoxymethylpenicillin may be associated with gastro-intestinal side-effects, they did not occur in these two patients, even with a prolonged course of treatment.

The two important considerations in the treatment of subacute bacterial endocarditis are the production of frequent high peaks of penicillin concentration in the blood (Finland, 1954; *Lancet*, 1954) and a prolonged course of therapy lasting at least four to six weeks (Bloomfield, 1950; Cates and Christie, 1951; Hunter, 1951), although satisfactory results have been claimed with shorter courses of penicillin (Hamburger and Stein, 1950). Among the factors predisposing to relapse is a short course of treatment (Cates and Christie, 1951). Whereas phenoxymethylpenicillin cannot produce penicillin blood concentrations comparable to those of parenteral penicillin, it does offer an easy and effective method of continuing therapy after discharge from hospital, and consequently of reducing the risk of relapse. With parenteral penicillin the difficulties associated with a prolonged course of out-patient treatment are self-evident.

Whereas the immediate results of therapy in both these patients have been completely satisfactory, long-term observation is required to see that these results are maintained. The first patient has been under observation for six months with no recrudescence of infection while on a prophylactic dose of 240 mg. four-hourly. The second patient is on the same prophylactic dose and has been followed up for two months after discharge from hospital.

Summary

The use of oral phenoxymethylpenicillin in two cases of subacute bacterial endocarditis due to a penicillin-sensitive *Streptococcus viridans* is described. In one case treatment was initiated with parenteral crystalline penicillin and maintained with phenoxymethylpenicillin for nine months, and in the other the oral preparation was used alone for three months. No gastro-intestinal or other side-effects occurred. The importance of penicillin blood concentrations and duration of treatment is considered.

We are indebted to Professor G. M. Wilson for his valuable help and advice, to Dr. J. Colquhoun and Miss E. C. Scorer, of the department of bacteriology, Sheffield Royal Infirmary, for carrying out the serum penicillin estimations, and to Sister Jean Tring for her generous assistance.

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DETERMINATION OF PEROXIDASE IN URINE

SIMPLE METHOD FOR ROUTINE EXAMINATION OF URINE FOR ERYTHROCYTES AND LEUCOCYTES

BY

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In diseases characterized by the presence of pathological amounts of erythrocytes and leucocytes in the urine (infections of urinary tract, tumours, calculi, nephritis, renal infarction, etc.) the correct diagnosis is generally easy if these cells or other protein are found in such quantity that a routine protein test is positive, indicating need for further examinations. If the number of cells is so small that the routine test is negative, microscopy of the centrifuged deposit will prove necessary for the diagnosis. When the symptoms do not suggest the diseases in question, however, this examination is often overlooked in routine consultation work, to the detriment of correct diagnosis. Unfortunately the local symptoms indicating the answer are fairly often absent. Infections of the urinary tract constitute an example in point, and they rank first among the diseases in question in regard to incidence.

At the Third Medical Clinic of the University of Helsinki an accurate routine examination was made of the urine of every female patient admitted. Infection of the urinary tract was diagnosed in 147 (13.1%) of 1,141 patients; symptoms suggestive of the disease were felt by only 35.4% of the patients in whom it was diagnosed (Halonen and Halonen, 1950). However, a routine examination calling for the centrifugation and microscopy of the urine is a fairly laborious task for the practising physician to perform for each patient. There should be a simpler method of determining the pathological erythrocyte and leucocyte count of urine.

Several methods of this type have been suggested. Caplan and Discombe (1951) made an analysis of the methods of estimating urine erythrocytes. Among the most recent methods applied in practice are Baron's (1951) modification of the *o*-tolidine test, Watson-Williams's (1955) tablet test, and the method of Balme *et al.* (1956) working on the same principle and enabling also the quantitative determination of erythrocytes. The last-mentioned method is based on the circumstance that iron-containing blood derivatives catalyse the oxidation of amidopyrine by hydrogen peroxide to produce a lilac colour.

I have found a method, which I believe is simpler than those suggested so far, of determining the presence of pathological quantities of erythrocytes and leucocytes in urine. As the results have proved good in practice, the method is here reported.

Method

This is based on the ability of the peroxidase ferment present in erythrocytes and leucocytes (also haemoglobin) to dissolve hydrogen peroxide. The volume of oxygen given off when hydrogen peroxide decomposes is dependent on the erythrocyte and leucocyte count of the urine sample. Bearing in mind the apparatus ordinarily available to the practitioner, I sought the simplest possible method of determining the quantity of this gas produced. The following procedure was evolved. The only reagent needed is 30% hydrogen peroxide. The apparatus is that employed in the conventional determinations of the erythrocyte sedimentation rate (Westergren).

Two ml. of urine is poured into the small tube. (No pipette is necessary, as it was found that the quantity need not be accurately measured.) It is most helpful if the tube has a 2-ml. graduation mark. Four drops of 30% hydrogen peroxide are then added, and the mixture is immediately put into the E.S.R. tube proper, up to the usual mark. It is advisable to do the stirring first, by drawing the mixture into the tube and expelling it several times. The height to which the liquid or any froth on it rises above the original graduation mark is read after 30 minutes in the usual manner in millimetres. No rise is found in a normal case.

This method I call the peroxidase amount determination (P.A.).

Controlling the Method

Result with Healthy Test Subjects.—The urine samples of 40 healthy persons (20 of both sexes), in which nothing pathological was found by microscopy of the centrifuged deposit, gave a P.A. reading of 0 mm. in 38 cases and 1 mm. in two cases (both females).

Controlling Accuracy of the Method

1. Given amounts of erythrocytes were added to the urine of six different males; the samples had shown a minimum of sediment when subjected to routine examination. A comparison was made between the different erythrocyte dilutions and the P.A. readings obtained. The procedure was repeated, using 0.9% sodium chloride solution as erythrocyte diluent. The results are shown in Table I. The P.A. reading was over 1 mm. (positive) without exception in samples with an erythrocyte count of over 25/c.mm. Samples with 10 and 20/c.mm. gave an uncertain positive result (P.A. 1 mm.) in two out of six cases. Samples with 25/c.mm. likewise gave an uncertain positive result (1 mm.) in one case out of six and a positive result (2 mm.) in one case; in the other cases the result was negative. The results were even clearer in sodium chloride solution. Over 25 erythrocytes per c.mm. always gave a positive result. With this amount and quantities below it the result was without exception negative.

2. The effect of the urine leucocyte content on the P.A. value was examined by preparing dilution series from urine containing a number of leucocytes but no other cell elements. In addition to the P.A. determination, routine microscopy of the centrifuged sediment was also performed on the samples of these series. The results are shown in Table II. The P.A. values corresponded fairly well with the dilution ratios—even better than the results given by microscopy.

TABLE I

Erythrocytes per c.mm.	Turbidity of Urine	Test for Urine Protein	P.A. Readings (mm./30 min.). Minimum and Maximum Value from Six Different Series
5,000	Turbid	Positive	100 * (100)
2,500	Slightly turbid	Negative	100 † (100)
1,000	Clear	,,	100 ‡ (100)
500	,,	,,	26–39 (33)
250	,,	,,	12–26 (24)
100	,,	,,	5–19 (6)
50	,,	,,	2–12 (2)
25	,,	,,	0– 2 (0)
20	,,	,,	0– 1 (0)
10	,,	,,	0– 1 (0)
8	,,	,,	0– 0 (0)
5	,,	,,	0– 0 (0)

Figures in parentheses are the results with 0·9% NaCl solution instead of urine (mean).
* Maximal value reached in ½–2 minutes. (In NaCl solution, 32 sec.).
† Reached in 3–6 minutes (NaCl, about 5 minutes).
‡ Reached in 6–10 minutes (NaCl, about 11 minutes).

TABLE II.—*Effect of Quantitative Dilution of Urine Containing About 800 Leucocytes per c.mm. on the P.A. Reading*

Leucocytes per c.mm.	P.A. Reading	Leucocytes per Field of Vision (Enlargement × 290) in Microscopy of Centrifuged Deposit (Mean Value from 10 Counts)
800	100*	40·1
100	45	12·4
50	25	7·2
25	9	4·2
20	5	2·9
5	0	1·0

* Maximal value reached in 10 minutes.

TABLE III.—*Relation of P.A. Readings to Microscopy of the Centrifuged Deposit*

Erythrocytes or Leucocytes per Field of Vision (Enlargement × 200) by Microscopy of Centrifuged Deposit	No. of Cases	P.A. Readings (mm., 30 Minutes)			
		0	1–2	3–10	11+
		No. of Cases			
0– 3	47	35 (1)	6	—	6 (5)
4– 9	36	13 (1)	13	6	4 (3)
10–20	11	—	2	6 (2)	3 (3)
21+	24	—	2	2 (1)	10 (10)

Figures in parentheses are numbers of cases with positive urine culture.

3. In 117 urine samples sent to the hospital laboratory the results obtained by microscopy of the centrifuged deposit and the P.A. reading were compared. Bacterial cultures were also made from the same urine samples. Table III shows the results. It brings out the general correspondence between the microscopy and P.A. determinations, and also reveals that in individual cases there was some inconsistency. At the top of the right-hand column are presented the six cases in which microscopy gave a normal result and P.A. a high reading (at least 11 mm.). The positive culture in five out of these six cases (*Escherichia coli* was found in 3, *Proteus mirabilis* in 1, enterococcus in 1) supports the reliability of the P.A. value. It is worthy of note that in three of these cases the microscopist stated that the sediment contained a considerable amount of urate precipitate, which, as is well known, hampers the examination of sediment. Furthermore, the sixth case had suspected nephrolithiasis.

The results with a P.A. of 0 mm. call for comment. Urine culture is stated to have given a positive result in two cases. In one of these the first culture was positive (*Pr. mirabilis*). However, when the culture was repeated the result was negative, although the patient had had no treatment. She was also symptom-free in regard to the

urinary tract. In the other case *E. coli* was found, as had occurred in the earlier sample. Repeated culture gave a negative result. The patient had, however, received sulpha preparations continuously.

Discussion

The first question in the assessment of a test for the determination of urine erythrocytes and leucocytes is whether it is sensitive enough. Normal urine is thought to contain a maximum of some 20 red cells per c.mm. For normal adult males the content is no more than two red cells per c.mm. (Larcom and Carter, 1948). Watson-Williams (1955) estimated the red-cell content to be about 10 times as great in women. The P.A. test was either 0 or 1 mm. if the quantity of red cells in question was 25 or fewer per c.mm. A larger red-cell count invariably gave a higher reading. With regard to erythrocytes, then, the P.A. test can be regarded as sensitive enough to indicate pathological amounts of red cells in urine. The value 0 mm. is negative, 1 mm. is uncertainly positive, 2 mm. and over positive. The reading gives a sufficiently good idea also of the quantity of red cells. As regards leucocytes, the same conclusions are warranted on the basis of the tests performed (Tables II and III). Normally fewer than 10 leucocytes are present per c.mm of urine (Dukes, 1939). Five leucocytes per c.mm. gave a P.A. reading of 0 mm.; when there were 20 leucocytes per c.mm. the reading was 5 mm.

A weak point, of course, is that the test does not differentiate between erythrocytes and leucocytes, which still has to be done by microscopy. As already pointed out, haemoglobin also gives a positive reaction, since it contains peroxidase. This weakness notwithstanding, I find it suitable for routine examination on account of its simplicity and reliability. Opinions may naturally differ over the necessity for routine urine examination for erythrocytes and leucocytes. However, infections of the urinary tract alone are so common, especially in women, that some such examination seems necessary. Halonen and Halonen (1950) found these infections in 13.1% of female hospital patients. In two Amsterdam hospitals the figure was 29% (Loopuyt, 1946). Jäämeri (1943) found in 600 pregnant or puerperal women that 29% in pregnancy and 21% in puerperium had an infection of the urinary tract. The early diagnosis of this infection has an added importance to-day, when the facilities for its treatment are better than before. Only thus is it possible to avoid the development of numerous cases of nephrocirrhosis pyelonephritica.

The procedure in the P.A. test was arrived at empirically. Great emphasis was laid on making even moderately pathological amounts of red cells and leucocytes in urine give the strongest possible peroxidase reaction. For instance, hydrogen peroxide solutions were experimented with in 3, 10, and 30% dilutions. The quantities used in the tests varied from 1 drop to 2 ml. Although 4 drops of 30% hydrogen peroxide was finally decided upon, it was observed that 3–7 drops gave nearly the same result. Actually this means that the urine sample taken in the small tube need not be measured with particular accuracy. Thirty minutes was established, also empirically, for the reading of the P.A. value. A further increase in the value often occurred between 30 and 60 minutes, but it was slight. The maximum was often reached before 30 minutes: in fact, the qualitative and to some extent even the quantitative result can be indicated within some 20 seconds of taking the sample into the tube. The formation of gas bubbles in the tube points to the presence of an increased amount of peroxidase, and the rate of bubble formation is in relation to its quantity. In 20 seconds 50 red cells per c.mm. have already produced a distinct bubble formation.

Clearly, a more accurate result would be possible in peroxidase determinations if the volume of gas given off could be ascertained more exactly. Indeed, it is obvious that when the above procedure is used the quality of the urine —for instance, surface tension—affects the result, as was shown in Table I. The amount of gas given off was easy to determine in the tube apparatus employed in the sugar fermentation test. Greater stress was laid, however, on simplicity of method than on small gains in accuracy.

Summary

A simple method has been evolved for the preliminary determination of the quantity of erythrocytes and leucocytes in urine. The amount of peroxidase contained in erythrocytes and leucocytes (haemoglobin) was estimated with an ordinary E.S.R. apparatus. The only reagent needed was 30% hydrogen peroxide. The accuracy of the method was assessed as satisfactory for the practical requirements of clinical work.

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CARBUTAMIDE IN TREATMENT OF SCHIZOPHRENIA*

BY

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Carbutamide (BZ.55), appearing to act as a euphorizing anti-hallucinogen, has given encouraging results in the treatment of 60 patients with schizophrenic illness, 45 of whom left the mental hospital recovered or relieved. The drug was originally introduced by Achelis and Hardebeck (1955) as an oral hypoglycaemic substitute for insulin in the treatment of diabetes, and was known to produce euphoria in normal healthy subjects (Franke and Fuchs, 1955).

I have already described a tentative application of carbutamide to psychiatric cases (Frost, 1957), and the present communication gives substance to the value of this drug as an anti-hallucinogen in schizophrenia.

Administration.—On the first day—a test day—a fasting blood-sugar is estimated; three 0.5-g. carbutamide tablets are given and the patient takes no food for one hour, when a further blood specimen is withdrawn for glucose estimation. The patient is then given food and glucose. Three 0.5-g. carbutamide tablets are thereafter given for not more than three successive days a week, followed by a drug-free interval of four days. This regime is repeated for four weeks only. Except on the first test day, the tablets are given with ½–1 oz. (14–28 g.) of glucose in a drink of water or mineral water, and the patients are encouraged to take glucose *ad lib.* throughout every day of the course and for two weeks after. *The hypoglycaemic effect of the carbutamide is to be avoided during treatment.* Patients should be kept under hospital observation for two weeks after the end of the course.

Results

Of 60 patients, 45 were discharged recovered or relieved. Of seven subsequently readmitted, four left hospital again after a second, shorter, course of carbutamide.

*Based on a paper read to the second International Congress for Psychiatry, Zurich, September, 1957.

In schizophrenic illness superimposed upon mental defect or intellectual retardation the psychotic episode was cut short and restoration to home life effected. Hallucinosis could fade quickly, sometimes in a few days, or could linger till the end of the course; depression would lift in a rather more steadily progressive manner, and was often replaced in the third week of treatment by euphoria. Of poor prognostic omen were agitation and tension in the schizo-affective cases, and, of course, obsessive cases did not do well. If the blood-sugar level rose instead of falling as expected on the first test day the outlook was ominous. No death occurred in this series.

Two groups of cases were covered: group 1 consisted of first admissions treated by carbutamide alone (30 cases); group 2 consisted of 30 cases treated by drastic physical methods (deep insulin coma in 17 and E.C.T. in 13) in a previous or during the present admission before recourse was had to carbutamide. In group 1 (naturally the most recent cases with shorter histories) 26 were alleviated; in group 2, 19 improved.

In this study, 54 cases had less than a 12-months history: in six instances attacks had occurred two to six years previously. Table I gives a summary of the clinical groups concerned.

TABLE I

Diagnostic Groups of Schizophrenia	No. of Cases	Recovered	Relieved	Not Improved
Simple hebephrenic ..	20	9	5	6
With mental defect ..	4 } 8		4 } 8	
With backwardness ..	4 }		4 }	
Paranoid states ..	11	4	4	3
"Schizo-affective" ..	15	8	4	3
With obsessive features ..	6		3	3
Totals ..	60	21	24	15

Teenage Hebephrenes.—Of seven teenage hebephrenes, five did well on carbutamide. All exhibited hallucinosis, fatuity, suicidal behaviour, and neglect of the person. These five lost their hallucinations, were no longer suicidal, spoke relevantly, and departed neat and presentable youths. One left to resume grammar-school study; another has taken up decorating work; a third certified patient, who "escaped" from hospital, absconded from home (the parents not knowing his whereabouts), but managed to find himself work, saved £80 in two months, and returned safely to his family, welcomed as warmly as any prodigal son.

Mental Defectives with Superimposed Schizophrenic Illness.—Four cases in this series were mentally defective. Aural hallucinosis was coupled with unemployability in all cases; one was apprehensive, and another was excited and aggressively impulsive. In addition there were four dull intellectually backward patients in whom a schizophrenic illness was successfully treated. All, defective and retarded, went home relieved.

Paranoid Cases: Psychotherapeutic Openings.—Carbutamide renders paranoid schizophrenics accessible to psychotherapy in a state of clear consciousness untrammelled by hallucinosis, depression, or though blocking. Hallucinosis might go, but a suspicious frame of mind could persist. In one case a Nigerian male nurse was asked, as were all the staff, about 30s. missed by a patient. The nurse thought accusations of theft were being levelled particularly against him, even though the money was found in half an hour in the patient's discarded linen. The nurse thought someone else had placed the money to spare the nurse's conviction. An acute schizophrenic reaction followed with accusatory hallucinosis and fear of death. The acute phase passed quickly with carbutamide therapy. The nurse resumed his nursing work, but suspected that he was being supervised and was not being given sole charge because he had been in a mental hospital. But he could see the possibility that perhaps a "cautious" policy was explicable in the light of his mental breakdown—and, for the first time, faced the issue of going back home as a solution hitherto precluded on grounds of pride and "face-saving."

Toxicity Tests and Precautionary Measures

Agranulocytosis, thrombocytopenia, and a toxic effect on the liver were the risks most feared by those who used carbutamide for its oral hypoglycaemic effect in diabetes. Therefore counts were routinely made of white cells and thrombocytes; also a liver turbidity test.

In this series no death occurred; no leucopenia; and in only two cases was there a temporary drop in the thrombocyte count.

TABLE II.—*Correlation Between Serum Sulphonamide and Blood-sugar Levels*

	Case 1	Case 2	Case 3
Total serum carbutamide (mg./100 ml.)	24·2	27·2	29·0
Free (mg./100 ml.)	12·1	10·9	11·7
Bound	12·1	16·3	17·3
Fasting blood sugar (mg./100 ml.) ..	73	61	65
1 hour after carbutamide (mg./100 ml.)	45	42	34
1½ hours	42	38	34
2	45	68	38

As glucose was given freely throughout treatment, hypoglycaemic reactions were slight (sweating, giddiness), and only occasionally was it necessary to give it intravenously (10–20 ml. of 50% glucose sufficed).

Barbiturates were forbidden, lest the risk of agranulocytosis was increased. Bone-marrow soup was given daily as a prophylactic against agranulocytosis.

Three illustrative cases are reported. The correlation between serum sulphonamide and blood-sugar levels is shown in Table II.

Case 7

A boy aged 15 (school leaver) was admitted to hospital on October 24, 1956. On admission he was neglected and unkempt. His conversation was disconnected. His mind, he stated, was muddled and confused. He had thoughts of taking his life. He said, "I shall cease to live." He heard voices of men and of women. He wept. Genetically loaded: mother certified. He was given tranquillizers; electric convulsion treatments (17); also deep-insulin-coma therapy. He was incontinent, salivated, and held his food in his mouth without chewing. Later he began to refuse food. He was found sitting in a washbowl masturbating, with his feet in another washbowl. Owing to risk of malnutrition and its effects, the carbutamide was given with glucose in the tube feed.

On January 31, 1957, he was no better, and carbutamide was discontinued. Electric convulsion treatment was recommenced—six were given between February 1 and 18. He improved slightly, only to relapse on March 15 with hallucinations.

On March 25 carbutamide with glucose was given. He responded well, lost his hallucinations, spoke relevantly, and began to occupy himself. He left hospital on April 17 and took a job. When seen on a follow-up visit he had clearly "recovered." W.B.C., 7,600/c.mm.; thrombocytes, 214,000; thymol turbidity, less than 1 unit.

Case 8

A male student aged 17 was first admitted to Deva Hospital on August 3, 1956, mute, resistive, and uncooperative. He showed mannerisms and grimaced. He heard noises in the head and a voice. He made sudden dashes, only to stop suddenly, standing in a fixed position. E.C.T. and deep insulin coma gave no benefit. He departed, "not improved," on November 7. Diagnosis, schizophrenia.

He was certified on December 6, being manneristic; he grimaced, made fatuous remarks, and was aggressive. Tranquillizers had little effect. He subsequently escaped twice,

to be brought back. Psychological report on December 24: verbal I.Q., 108; performance I.Q., 92; full-scale I.Q., 101 (Wechsler Bellevue Scale).

Mental deterioration: a net loss 11%—Rabin's ratio. Giggled and grimaced. Was listless, retarded, bizarre, had difficulty in verbalizing, and lacked insight. His M.M.P.I. T score for schizophrenia was 96, indicating a fairly advanced cluster of schizophrenic symptoms.

On March 18, 1957, his fasting blood sugar was 80 mg./100 ml.; one hour after the drug it was 68 mg./100 ml. Carbutamide was given; his behaviour improved, he began to show insight, and lost his mannerisms. He became occupied, but while on leave he absconded altogether and was discharged by escape on August 5. Two months later he returned home, having by his own labour saved £80. He said he had gone away to prove that he could fend for himself.

Case 9

A youth aged 17 was admitted as a voluntary patient on September 16, 1957. He had previously been a patient for two weeks in February, 1957, and been given E.C.T.

On admission on the second occasion he was extremely frightened. He also cried and laughed irrelevantly, and seemed to be preoccupied, in a listening attitude, with auditory hallucinatory experiences. A duly authorized officer reported on February 6 that the patient had never made progress at school, and over the past two months had made references to the people on television, sitting in a corner.

Psychologist's report on September 18: verbal I.Q., 61; performance I.Q., 60; full-scale I.Q., 60 (mental defective) (Wechsler Bellevue Scale). A further report on October 17 showed: verbal I.Q., 57; performance I.Q., 64; full-scale I.Q., 60 (mental defective). He made some effort in direct-stimulus response situations, but failed where conceptual thinking was required. On November 11 the report was: verbal I.Q., 73; performance I.Q., 90; full-scale I.Q., 79 (less 10% practice effects, 71—borderline). He was reassessed on a new scale—the Wechsler adult intelligence scale. The validity was checked by the administration of the progressive matrices (Grade V=intellectually defective). He would be capable of working only in a non-competitive environment under supervision.

On September 23 his fasting blood sugar was 90 mg./100 ml. One hour after the drug it was 80 mg./100 ml. On October 8 the W.B.C. was 7,600/c.mm.; thrombocytes, 357,000/c.mm.; thymol turbidity, less than 1 unit.

The diagnosis in this case was a schizophrenic illness superimposed upon mental defect. He was placed on carbutamide and the schizophrenic illness responded well; he lost his hallucinations and fear, and was able to work to the full limits of his limited intelligence. There is every hope that a place will be found for him at a Remploy factory.

Summary

Of 60 schizophrenic patients treated with carbutamide, 45 were sent home recovered or relieved. Carbutamide has proved a safe drug when used for four weeks with drug-free intervals. No death occurred in this series.

I acknowledge the help of Mr. H. V. Ridpath, who carried out the routine laboratory sugar and sulphonamide estimations and toxicity tests; the observation and care of the nursing staff, and Charge Nurse R. Lawson in particular; the general advice given by Dr. A. Grünbaum, whose experience of carbutamide at his diabetic clinic made me cautious about the toxic hazards. I thank the late Dr. L. J. Draspa for the results of clinical psychological assessments, and Messrs. Eli Lilly and Company for supplies of carbutamide freely given.

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Medical Memoranda

Case of Tuberculous Rheumatism

An association between tuberculosis and some forms of rheumatism has been much canvassed on the Continent since the work of Poncet at the turn of the century (see Poncet and Leriche, 1909). The literature has been reviewed by Brav and Hench (1934) and Hammes (1951). In Britain and America "tuberculous rheumatism" has never been generally accepted as an entity, and Brav and Hench (1934), who add a statistical and pathological study of their own to a critical review of the literature, consider that no unequivocal proof has ever been produced for the existence of such a disease. Sheldon (1946) says: "There can be no doubt that such cases [of tuberculous rheumatism] exist . . . although cases reported in English writings are so rare that the condition in this country must be either very uncommon or possibly overlooked." He reports six cases, all in children, seen in eight years, and refers to three cases reported by Findlay in 1920, also in children. Dalgleish (1952) reported a doubtful case. This paucity of cases in the English literature prompts me to record the following history.

Case Report

In January, 1956, a pilot then aged 25 had a small haemoptysis. At about the same time he developed a rash on both legs which was ultimately diagnosed as a papulonecrotic tuberculide. A few days after the haemoptysis he complained of pain and stiffness in the right ankle, followed by similar symptoms in the left ankle after another two days. He also noticed at this time a swelling in the left side of his neck. On February 6 the positive clinical findings were the rash, enlargement of glands below the left mandible, effusions into both knees, and swelling and stiffness of both ankles. Chest *x*-ray examination showed no abnormality, the E.S.R. was 23 mm. in one hour, and the Mantoux reaction was positive at 1/10,000. On bed rest and large doses of aspirin his symptoms disappeared and his joints returned to normal in one week. Two weeks after the beginning of treatment his E.S.R. was 6 mm. in one hour and the aspirin was stopped.

In April a sterile left cervical abscess was drained; biopsy of the abscess wall showed no diagnostic features, and no tubercle bacilli were seen on direct smear of the pus. Tonsillectomy was carried out in May.

Apart from his rash, which persisted, he remained well until February, 1957, when a swelling developed above the left clavicle. This was excised, and found to be a caseating tuberculous gland. Late in June he developed right-sided pleuritic pain and a mild pyrexia. Chest *x*-ray examination then showed a small right pleural effusion. He was admitted to hospital six days later, by which time he was symptom-free and afebrile, and *x*-ray examination showed complete disappearance of the effusion, with clear lung fields. The tuberculide was present on both legs, and he had crepitus in both knees. The E.S.R. was 2 mm. in one hour, *x*-ray films of the knees and ankles showed no abnormality, and biopsy of the parietal pleura on the right showed non-specific fibrous thickening.

Comment

This man shows a picture of prolonged yet essentially benign tuberculous involvement of lymph nodes and skin, associated with two episodes of fleeting inflammation of serous membranes, once in the knees and ankles and once in the pleura. No doubt many of the reports on "tuberculous rheumatism" deal with cases of frank tuberculous arthritis, or else with acute rheumatic fever or rheumatoid arthritis coincident with tuberculosis elsewhere in the body. Sheldon (1946) maintains that there remains a core of cases in which fleeting rheumatic symptoms and signs are intimately associated in time with acute tuberculosis elsewhere in the body. He emphasizes that such joint involvement is found on close analysis to be unlike that of acute rheumatic

fever or acute rheumatoid arthritis, and stresses its brief duration in the tuberculous cases. The case reported here would appear to fulfil these criteria. It is interesting to recall in this connexion the well-authenticated syndrome of erythema nodosum, arthralgia, and hilar lymph-node enlargement, which is a common presentation of sarcoidosis (James *et al.*, 1956). The association between pleurisy and "tuberculous rheumatism" has been described by Poncet (1902) and Schneider (1903). As in the case of tuberculous rheumatism itself, it is not possible to evaluate many of these older reports in the light of the stricter diagnostic concepts of to-day.

I am grateful to the Director of Medical Services for permission to publish.

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Case of Behçet's Syndrome with Neurological Involvement

The association of relapsing iritis, oral ulceration, and genital ulceration has been known for some time, and in 1937 Behçet suggested that the triad forms a specific disease. It is now recognized that the condition has wider manifestations and that these may include skin lesions, arthralgia, thrombophlebitis, and neurological lesions. The case reported here is another example of Behçet's syndrome with neurological involvement.

CASE REPORT

The patient was a married woman aged 42 with two grown-up children. Her past history included operative repair of a right convergent strabismus, which had been present since birth, and an isolated attack of thrombophlebitis of the left leg in 1950. In the middle of March, 1956, she developed severe, persistent pain in the left shoulder region. She attributed the pain to a heavy fall on the left shoulder, but there had been an interval of several days between the fall and the onset of the pain. *X*-ray examination of the shoulder was negative and she was given a course of physiotherapy at another hospital, but without much relief. Two weeks later she noticed dysuria and soreness of her vulva on walking, and discovered an ulcer about the size of a penny on that organ. This was followed by the development of small, slightly painful ulcers on the mucous membranes of her lips. A few days later, whilst out walking, her legs felt very weak and she had to be assisted home. The right leg improved overnight, but paralysis of her left leg persisted, and on the following day she noticed that her left arm also was paralysed. At this stage, April 16, she was admitted to Paddington General Hospital.

Examination showed a pale, middle-aged woman who was co-operative but rather depressed. She had a left hemiparesis of severe degree with increased deep reflexes on the left, an extensor plantar response, and absent left abdominal reflexes. There was no sensory loss. Two small ulcers were seen on the mucous membrane of her lower lip, and on the right labium minorum there was a shallow, circular ulcer about ½ in. (1.3 cm.) in diameter with a granulating base. There were no palpable inguinal glands. Her blood pressure was 145/90. The C.S.F. findings were: normal pressure; lymphocytes, 64/c.mm.; protein, 60 mg./100 ml.; no excess of globulin; chlorides, 720 mg./100 ml.; and negative Wassermann and Kahn reactions.

Over the next few days her symptoms and signs progressed and she complained of dizziness, blurring of vision, difficulty in swallowing, and a numb feeling over her tongue, lips, and nose. Examination on April 25 showed gross horizontal nystagmus on lateral fixation and spontaneous vertical nystagmus, more rapid on elevating the eyes. Both corneal reflexes were diminished, particularly on the left, and there was slight diminution of pain sense over the right forehead. Bilateral facial weakness was present, more marked in the upper face on the left and in the lower face on the right. Taste was defective over the anterior two-thirds of the tongue. There was right palatal weakness. She had a feeble cough and dysarthria which appeared to be a combination of pharyngeal weakness and cerebellar disturbance. There was weakness of the left trapezius and sternomastoid. Her left hemiparesis remained unchanged.

In view of the rapidly developing bulbar signs the patient was transferred to the respiratory unit at the National Hospital for Nervous Diseases, Queen Square. A repeat examination of the C.S.F. performed there showed a fall in the lymphocyte count to 13/c.mm. and a slight increase in protein to 95 mg./100 ml. No further deterioration in her condition occurred and the use of a respirator was not required. She was kept under observation and her brain-stem signs diminished considerably, her hemiparesis improved, and the ulcer on her vulva healed. When she was transferred back to Paddington General Hospital on May 11, she was able to walk, but the weakness of her left arm remained severe. The only abnormalities of her cranial nerves were a slight left lower facial weakness and slight nystagmus on extreme lateral fixation.

She was discharged on June 7, and the recovery from her hemiparesis has continued. She has since had further ulcers on her lips and buccal mucosa from time to time, but no further genital ulceration. In October she described several small skin lesions which appeared on her left arm, left shin, and right groin. These apparently started as vesicles which broke down and left small ulcers which persisted for a few days. There has never been any abnormality of her eyes.

COMMENT

Although only two of the features of the "triple syndrome" complex are present this is accepted as being sufficient for the diagnosis of Behçet's syndrome (Curth, 1946; Phillips and Scott, 1955). Eye involvement may not occur until as long as 10 years after the initial manifestations.

Neurological complications usually occur between the second and fifth years of the disease, and only in the first case of Wadia and Williams (1957) has the history been as short as three months. The illness here reported appeared to have an acute onset, with pain in the region of the left shoulder-joint, followed by orogenital ulceration and leading in four weeks to severe neurological disorder.

As in many of the other reported cases, this patient's signs were those of a mid-brain lesion. Her case is of particular interest in that she showed sensory changes and cerebellar signs, both of which appear to be uncommon in Behçet's syndrome. There seems to have been involvement of the cerebellar tracts in the mid-brain, the sensory nuclei of the trigeminal nerve, and the facial nuclei. An interesting finding was the defective taste sensibility, pointing probably to a peripheral nerve lesion.

Pallis and Fudge (1956) pointed out that the neurological disorder usually conforms to one of the following patterns: (1) a brain-stem syndrome, (2) a meningomyelitic syndrome, and (3) an organic confusional syndrome. This classification was based on the 11 cases previously recorded and two of their own, but as further cases have been reported (McMenemey and Lawrence, 1957; Evans, Pallis, and Spillane, 1957) it has become apparent that this classification is too rigid and that no case conforms entirely to one pattern.

I am grateful to Dr. Redvers Ironside for his advice and to Dr. T. A. Kemp for permission to publish the case report.

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Reviews

DYNAMICS OF ANXIETY AND HYSTERIA

The Dynamics of Anxiety and Hysteria: An Experimental Application of Modern Learning Theory to Psychiatry. By H. J. Eysenck. (Pp. 311+xiv; illustrated. 32s.) London: Routledge and Kegan Paul. 1957.

Since the appearance in 1947 of his monograph *Dimensions of Personality* Professor Eysenck and his growing team of psychologists at the Maudsley Hospital have steadily accumulated a mass of test results and experimental data from psychiatric patients and have explored the correlations between them with much statistical vigour. This is the fifth monograph of the series and describes the direction which this work is currently taking, the preliminary hypotheses which have been made on the facts observed, and the results of their submission, where possible, to experimental proof. It is an important book, for on this occasion the author has gone a good deal farther in the way of theory-building and has outlined the ways in which he thinks the scientific study of personality and the applications of learning theory can contribute to the problems of clinical psychiatry. The descriptive nosology of the psychiatrist and his habit, as a physician, of grouping patients by syndromes are necessarily complicated, at times vague and dependent on the development of a clinical intuition, because of the large number of variables which underlie the manifestations of maladjustment in any one human individual. Professor Eysenck has no time for vagueness and is always on the lookout to reduce clinical complexity. He feels that the present psychiatric approach, whether "dynamic," psychological, or descriptive, is getting us nowhere. The application of scientific method, statistical procedure, formal logic, and proof by experiment is for him the only way. He makes his case for a more detached psychiatry to replace the kindly inefficacy of present methods, and is in no doubt that the statistically and experimentally trained clinical psychologist should ultimately take responsibility for a large part of the field. Beside the prodigious industry, painstaking computation, and merciless experiment of his team the average psychiatrist seems a mere sentimental dabbler in problems of human distress. In this brave new world, history-taking and diagnosis are replaced by the test-situation, the questionary, and the statistical formula.

The book is complete in itself as a statement of the views of this group, for the conclusions of the previous monographs are recapitulated and then taken as the starting-point for the new postulates which are the main feature. It has been shown, for instance, by Professor Eysenck himself in a previous statistical study that patients receiving psychotherapy fare no better than those left on the waiting-list. From this the conclusion is intimated that the medical psychologist is never able to alter his patient's condition permanently for the better by mere words. This is an entirely different matter. If taken too literally, Professor Eysenck would destroy any confidence a clinician might have in his own experience and common sense by telling him that such things are not science, and by a display of statistical procedure far beyond his comprehension and which he can only carpingly suspect.

The book contains a remarkably full account of the previous work which has contributed to the present studies, and each aspect, statistical, methodological, and experimental, is fully covered, and it is thus a valuable source-book. There is a wealth of criticism of previous theory, but this is by no means all destructive, and postulates are put forward whereby the results of the work of Pavlov and Clarke Hull, in particular, can be evoked to explain deviant trends and might be applied, in conditioned extinction and other methods of treatment, to rectify the effects of an indifferent constitution or an unkind environment. Throughout a rigorous logic is applied, with hypothesis and fact carefully distinguished.

We are now aware of Professor Eysenck's aims—and these are wide, for he carries his predictions beyond the clinical scene into those of social structure and politics. After reading the book we have to decide whether his approach is going to alter the whole basis of abnormal psychology, and also whether some (but not all) of the basic assumptions are unjustified. At the moment we can only suspect these on the following general grounds. First, that it may not be possible to describe and classify the entirety of a human problem in terms of a mathematical formula, however brilliant the adaptations of canonical variate analysis and other procedures for extracting its essentials. If contact with the patient is limited to purely scientific exchanges predetermined by the scientist, something is likely to be missed. Secondly, that natural laws of permanent value, even if mathematically derived, can be stated in plainer English than is found here, so that their practical applications are evident. Thirdly, when science takes a step forward it is usually found that parts of pre-existing systems of explanation may still have some meaning and usefulness and can be integrated with the new. The next hypotheses to be tested are likely to be those which Professor Eysenck puts forward about psychological treatment, for here he will be returning to the clinical situation from which his work seems at times to have become so remote. The next monograph will be awaited with interest.

Clinical psychiatrists may feel it their duty to examine Professor Eysenck's approach for themselves, for, even if his theories have to be modified, the applications of learning theory which he has used have for some time cried out for clinical extension. For this they will need perseverance, for the treatment of the subject is thorough and serious, with no concessions to those who like an easy narrative. Humour is confined strictly to certain heavy-handed statements in the introduction. This may be science, but it is very cold psychiatry.

ALEXANDER KENNEDY.

ESSENTIALS OF CHEMICAL PATHOLOGY

Essentials of Chemical Pathology. By D. N. Baron, M.D. (Pp. 247+xii. 25s.) London: English Universities Press Ltd. 1957.

The publication of a new textbook is always an event of interest, and this one has the added advantage of dealing with a rapidly advancing subject. The author has designed it to meet the needs of medical students, house officers, and registrars, and it appears to be admirably adapted to this purpose. It does not set out to be a laboratory textbook, as the only practical details given are those for routine ward testing of urine and faeces. Since the major part of the writing was presumably done while Dr. Baron was working at the Courtauld Institute of Biochemistry, the book may be taken as representing the current practice at that institute. There is an introductory note by Sir Charles Dodds.

The arrangement of material follows established lines and represents a compromise between the chemical and pathological approaches. Thus the opening chapters treat of chemical topics, such as water, electrolytes, carbohydrates, proteins, and lipids, while the later chapters deal with tests applying to individual organs in the body. The accent everywhere is upon interpretation of biochemical data, and the book may therefore be said to have a rather wider appeal than intended, and could be read with advantage by all doctors interested in metabolic considerations. It is well written, and conveys a large amount of information in a form which is easy to absorb. The advanced student may perhaps be disappointed in the paucity of references, the only ones given being to other textbooks, but we are told in the introduction that the omission of literature references was intentional. The book is a convenient size of just over 200 pages and represents a useful addition to the literature on chemical pathology. It should prove invaluable reading for the purposes indicated, and seems likely to have a wide appeal to all interested in the biochemical aspects of disease.

N. F. MACLAGAN.

POPULATION PROBLEMS

The Human Sum. Edited by C. H. Rolph. Preface by Lord Simon of Wythenshawe. Illustrations designed by Alfred G. Wurmser and a cartoon by Vicky. (Pp. 232+vi; illustrated. 18s.) London, Melbourne, Toronto: Heinemann. 1957.

Published for the Family Planning Association to commemorate its 25th anniversary, this fascinating book consists of eleven essays by eminent writers on population, extending downwards from the world as a whole to the family and the individuals composing it. After a preface by Lord Simon of Wythenshawe, C. H. Rolph ably introduces the subject and each of the writers. Julian Huxley surveys the world scene with first-hand observations made during a recent world tour, and concludes that, in addition to a vast increase in the exploitation of the world's resources, population limitation by the underdeveloped countries is essential. This theme is reiterated by Bertrand Russell, who considers that "nothing is more likely to lead to an H-bomb war than the threat of universal destitution through over-population." The paper by A. S. Parkes is concerned with what the medical scientist, having been responsible for explosive population growth through effective death control, must now do to counterbalance it with equally effective birth control. Mary Stocks describes the history of family planning in Great Britain. C. H. Rolph contrives to infuse the Law's regard for the family with immense hilarity. Jacquetta Hawkes puts the case for intelligent family planning as against a constant succession of unwanted pregnancies. Michael Young and Peter Willmott contrast the horrors of the working-class families in East London 40 or more years ago with the encouraging enlightenment of the present day. Edward Blishen writes from his personal knowledge as a schoolmaster of the effects of parental attitudes—especially in regard to family planning—on the character of the boys he has to teach in a working-class district school. J. M. Mackintosh discusses changing attitudes within the family. James Lansdale Hodson gives a lurid account of induced abortion, with a plea for a more lenient attitude towards it on the part of the Law. Finally, the Reverend Sherwin Bailey discusses some theological considerations of marriage and the family; certain of his metaphysics read rather strangely after the factual accounts in the earlier parts of the book, but he concludes that the time has come for the Church to revise some of its ideas of sex.

The book is liberally illustrated with amusing line drawings by Alfred Wurmser and a cartoon by Vicky. Without doubt this book is an important social document, and the Family Planning Association is to be congratulated for having sponsored it.

G. I. M. SWYER.

INTERPRETATION OF ELECTRO-CARDIOGRAMS

Clinical Electrocardiography: Interpretation on a Physiologic Basis. By Manuel Gardberg, M.D. With chapters by Richard Ashman, Ph.D., Irving L. Rosen, M.D., and Louis Levy II, M.D. (Pp. 315+xi; illustrated. 95s.) London: Cassell and Co. Ltd. 1957.

Clinical Electrocardiography sets out to explain the matter on a truly physiological basis. The introductory part is therefore rather long and might become tedious, but it is nevertheless important and essential to study. Chapter 5, on the quantitative analysis of the QRS–T relationship, is not at all easy, but study of it will reveal the significance of the ventricular gradient: this is really well explained. Injury and then ischaemia are treated in great detail. Left and right bundle-branch block are considered in the conventional way. Coronary disease has a long chapter. In disturbances of the cardiac mechanism the theory of circus movement is accepted as the cause of flutter and fibrillation. At the end there is a chapter on vector cardiography; but the idea of the vector has already been introduced in the early chapters.

This book is profound and exhaustive, if not a little exhausting. The text does not always read easily. The print is in two columns and this tends to tire the eye. Not infrequently there are eight or more lines without a stop. There are numerous cardiograms and diagrams. The former are clear, but it would be simpler if only one complex was shown. The latter are apt to be so complicated and elaborate that they come near to defeating their object of making the text clearer, and their captions are extremely long. But if anyone can spend a very long time extracting the information, this book will certainly prove a prolific mine.

TERENCE EAST.

TREATMENT OF NEUROLOGICAL DISORDERS

Modern Therapy in Neurology. Edited by Francis M. Forster, M.D. Foreword by H. Houston Merritt, M.D. (Pp. 792. 90s.) London: Henry Kimpton. 1957.

A number of books on therapy have been published in recent years, but this is probably the first to be devoted to the treatment of organic neurological disorders. It is written by a group of American neurologists under the editorship of Professor Forster. As the editor says in his preface, there is increasing interest in the aetiology and therapy of diseases of the nervous system, and recent developments in neurochemistry hold promise of the discovery of more effective therapeutic methods. There is a good deal of information in this book about drugs which may be used in neurological therapy, but it is often difficult to discover from the text the indications for their use. The book would be of greater value if there was more information on the indications for and results of surgical treatment in some of the disorders which are discussed. On the whole the book is rather disappointing; certain chapters concerning diseases in which specific treatment is available, such as those on myasthenia gravis and meningitis, are good, but in some chapters the writing is diffuse and a large number of words seem to have been used to say comparatively little.

J. W. ALDREN TURNER.

MECHANISM OF RESPIRATION

The Respiratory Muscles and the Mechanics of Breathing. By E. J. Moran Campbell, M.D., Ph.D., B.Sc.(Lond.), M.R.C.P.(Lond.). (Pp. 131+xvi; illustrated. 20s.) London: Lloyd-Luke (Medical Books) Ltd. 1958.

This monograph of 119 pages of text contains an appendix and 16 chapters. It gives a very full and thorough account of each respiratory muscle and its anatomy. The movements of these same muscles and the mechanical factors underlying them are considered in some detail. The terminal part of the text includes an all too short account of the control of respiratory movements and the physico-chemical factors concerned in their regulation. In this portion the author reaches out to present a beautiful summary of modern, especially American, pulmonary medicine. This account is well illustrated throughout and largely based on the personal experimental findings of the author. The appendix treats of electromyography, its technique, its apparatus, and its record analysis. The field of medicine covered is not large, but it is important, and there is no book devoted to it in this country, and particularly at the postgraduate level, at which it will be valuable.

A. ST. G. HUGGETT.

The second volume of *Bibliography of Medical Reviews*, compiled at the National Library of Medicine, Washington, has appeared little more than a year after volume 1. It comprises subject references to about 1,800 review articles, mainly published in 1956, with a few dated 1955 and 1957. Material is taken exclusively from journals indexed in the *Current List of Medical Literature*. This bibliography will in future appear annually and from volume 3 will include an author index. It is published by the Superintendent of Documents, Government Printing Office, Washington, 25, D.C., U.S.A., price 60 cents.

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INTRAOCULAR PRESSURE

Twenty-five years ago the canal of Schlemm was regarded as a safety valve in the human eye, so that a rise of intraocular pressure above normal limits was counteracted by a flow of aqueous from the anterior chamber into the episcleral veins. Since that time the measurement of this outflow has been the subject of careful study, culminating in the development of methods whereby it can be accurately measured. W. M. Grant's tonography[1] and P. L. Blaxter's bulbar pressure test[2] can show, in a few minutes, whether the function of the drainage channels is below or above average, thereby enabling ophthalmic surgeons to treat their cases of glaucoma with some precision. Such studies have tended to divert the attention of workers engaged in research on the eye to the anterior chamber and particularly to its angle. Thus recent literature abounds in papers on gonioscopy, tonography, pathological changes in the angle of the anterior chamber, pressure changes in the episcleral veins, and so on. Indeed, further knowledge of the regulation of the intraocular pressure and glaucoma would almost seem to lie in a better understanding of outflow dynamics.

A reaction is setting in against this mode of thought, and two complementary lines of research are being followed to-day. The first is biochemical and has been quietly pursued by V. E. Kinsey[3] in the U.S.A. and M. E. Langham[4] in Great Britain. The discovery of the hypotensive action of acetazolamide ("diamox") in glaucoma[5] has led to a renewed interest in the chemistry of the eye and to the resuscitation of a theory of J. S. Friedenwald's[6] that a redox mechanism, maintained by enzymatic activity in the ciliary epithelium, is responsible for much of the secretion of the aqueous and provides energy for its flow. According to this theory, hydroxyl ions are generated continuously by the oxidation of reduced cytochrome oxidase in the ciliary epithelium, and the neutralization of these ions by carbon dioxide accounts for the excess of bicarbonate which is found in the aqueous and which gives it an osmotic pull higher than that of the blood. Acetazolamide acts by inhibiting carbonic anhydrase, the enzyme which normally controls the formation of bicarbonate. This theory, although questioned in points of detail,[7] suggests that the formation of intraocular fluid is due to a peripheral mechanism under local physico-chemical control. A failure in this control may theoretically produce a type of glaucoma which is due to excessive production of aqueous. Recently B. Becker and colleagues[8] published a series of such cases presenting raised intraocular pressure in association with a normal outflow as measured tonographically.

The second line of research stems from the supposition that there is a controlling central nervous centre, possibly in the hypothalamus. There are many clinical and experimental findings which are difficult to explain without this supposition,[9] particularly the consensual changes in intraocular pressure when alterations are induced in the fellow eye. This hypothesis has led D. P. Greaves and E. S. Perkins[10-12] to study the effects on the intraocular pressure of stimulation of the cervical sympathetic trunk and the third and seventh cranial nerves, and Perkins[13] to study the effect of stimulation of the fifth cranial nerve. Work has also been reported from various centres[14-18] on the changes in intraocular pressure resulting from stimulation of the central nervous system; in particular the diencephalon has received close attention, for this part of the brain is known to influence many bodily functions. J. Gloster and D. P. Greaves[18] give the results of their painstaking mapping-out of this area by stereotactic methods. Responses have been obtained showing independent variations of the intraocular pressure on stimulating points in the postero-dorsal region of the diencephalon and from a circumscribed area in the medial hypothalamus. The authors believe that their findings are compatible with the view that the diencephalon influences the intraocular pressure, but they do not allow the conclusion, as yet, that such influence is in the nature of a controlling mechanism. Both lines of thought require considerable experimental exploration. In the meantime it would seem desirable to study a series of cases of glaucoma in man wherein the outflow channels are functionally normal, for it may be possible in such a group to decide whether the anomaly in fluid formation and intraocular pressure is primarily neurogenic or biochemical, and whether centrally or peripherally determined.

[1] Grant, W. M., *Arch. Ophthal.* (*Chicago*), 1950, **44**, 204.
[2] Blaxter, P. L., *Brit. J. Ophthal.*, 1953, **37**, 641.
[3] Kinsey, V. E., *J. gen. Psychol.*, 1951, **34**, 389.
[4] Langham, M. E., in *Glaucoma Symposium*, edited by Duke-Elder, S., 1955.
[5] Becker, B., *Amer. J. Ophthal.*, 1954, **37**, 13.
[6] Friedenwald, J. S., ibid., 1949, **32**, Suppl. 9.
[7] Langham, M. E., and Lee, P. M., *Brit. J. Ophthal.*, 1957, **41**, 65.
[8] Becker, B., Keskey, G. R., and Christensen, R. E., *Arch. Ophthal.* (*Chicago*), 1956, **56**, 180.
[9] Duke-Elder, W. S., *Trans. ophthal. Soc. U.K.*, 1957, **77**, 205.
[10] Greaves, D. P., and Perkins, E. S., *Brit. J. Ophthal.*, 1952, **36**, 258.
[11] —— ibid., 1953, **37**, 54.
[12] *J. Physiol.* (*Lond.*), 1956, **134**, 393.
[13] Perkins, E. S., *Brit. J. Ophthal.*, 1957, **41**, 257.
[14] Schmerl, E., and Steinberg, B., *Amer. J. Ophthal.*, 1950, **33**, 1379.
[15] Nagai, M., Ban, T., and Kurotsu, T., *Med. J. Osaka Univ.*, 1951, **2**, 433.
[16] Weinstein, P., *Ophthalmologica* (*Basel*), 1954, **127**, 164.
[17] Sallmann, L. von, and Lowenstein, O., *Amer. J. Ophthal.*, 1955, **39**, Suppl. 11.
[18] Gloster, J., and Greaves, D. P., *Brit. J. Ophthal.*, 1957, **41**, 513.

WRAPPED FOOD

The exposure on slabs and counters of foods to be consumed uncooked and their handling by ungloved assistants is a constant and disturbing reminder of how readily disease can be transferred by way of the things we eat. One solution to this problem is the efficient wrapping of food, so that it may be handled freely before it is taken home to be unpacked and consumed. But as soon as standards are raised to the point where shoppers recognize the undoubted benefits of having food wrapped, so then are new voices quite reasonably raised to question the possible dangers that such a technological advance might bring in its train. Old threats to health from bacteria are apt to be forgotten in this sudden crusade for protection from chemical contamination. It is not now a question of whether that sliced meat contained a few salmonellae from the fingers of the shop assistant suffering from some intestinal upset, but do those nicely wrapped slices now contain a few milligrammes of a chemical that can be shown in the laboratory to poison animals? Under the U.S. Federal Food, Drug, and Cosmetic Act, "a food is deemed to be adulterated if its container is composed in whole or part of any poisonous or deleterious substance which may render the contents injurious to health."[1] The law is not so clearly defined in this country, but obviously it is important to ensure that wrapping food does not protect it from one hazard only to incur another.

The danger from a food wrapping can only arise if the wrapping itself contains a toxic ingredient which migrates into wrapped food. This problem has recently been faced by the British Plastics Federation, which has issued a report of the toxicity subcommittee of its technical committee.[2] The first part of this report suggests methods of assessing the migration of any ingredient of a plastic from the wrapping or container into the food or drink contained within it. No reasonable criticism can be levelled against the conditions suggested for the test, though analytical chemists may well feel some doubt about their ability to measure the migration of many of the plasticizers and stabilizers listed in the appendix into such media as olive oil. To assess any hazard to the consumer the amounts of a substance that can migrate must be considered in relation to the toxicity of that substance. The report does its best to face up to the fact that "toxicity" is not a property that can be measured simply in the way that "melting point," "solubility," or other physical property can be determined. The section headed "Toxicity Quotient" undoubtedly suffers both from condensation and from this difficulty of combining chemical and biological data for the purpose of producing a useful index of "safety." The report concludes with an appendix and bibliography which are very unsatisfactory. The bibliography contains 55 numbered references of which only two are given in the text: the rest are probably related to the "Table of Toxicity," but this is not evident. This table follows a recent code suggested for the classification of food colours by the Food Preservatives Subcommittee of the Food Standards Committee.[3] It classifies all the additives at present likely to be useful in the fabrication of plastic wrappings as of low toxicity (A), for restricted use or about which doubt exists (B), and materials known to be toxic (C). Unfortunately no references are given, so that a potential user might find it difficult to get at the sources of information which told him that "tri tolyl phosphate" or "trixylyl phosphate" were toxic. While this is undoubtedly true of tri-*ortho*-tolyl phosphate, there is good evidence to exonerate the *meta* and *para* tolyl phosphates.[4-6] It would be interesting to know the evidence for the classification of butyl lactate as toxic, whereas butyl laurate is apparently safe. But, despite these criticisms, we must welcome the appearance of this report.

[1] Lehman, A. J., *Quart. Bull. Ass. Food Drug Off. U.S.*, 1954, **18**, No. 4.
[2] Publication No. 40, British Plastics Federation, 47–48, Piccadilly, London, W.1. Price 5s. net.
[3] Food Standards Committee Report on Colouring Matter, 1954, H.M.S.O., London. See *Brit. med. J.*, 1955, **1**, 158, and 1956, **1**, 220.
[4] Hunter, D., Perry, K. M. A., and Evans, P. V., *Brit. J. ind. Med.*, 1944, **1**, 227.
[5] Aldridge, W. N., *Biochem. J.*, 1954, **56**, 1185.
[6] Hine, C. H., *et al.*, *J. Pharmacol. exp. Ther.*, 1956, **116**, 227.

DISEASE EDUCATION BY THE B.B.C.

The B.B.C. has decided to televise live operations in a series entitled *Your Life in Their Hands*. Why? The answer has been given by Mrs. Mary Adams, assistant to the Controller of Television Programmes, who, according to a press report,[1] said, "Our viewers have a healthy interest in disease which we feel it is legitimate on our part to satisfy." The producer of the series is reported to have said, "Nothing will go on the air which is not approved by the hospital from which it is coming. Patients are co-operating and their written consent to appearing is being obtained." It will be a strong-minded patient who has the courage to refuse to give his permission, and to impose on him this extra burden of decision at a time when the anxiety of a patient is at its height is unwise. The B.B.C. seems to be proud of the fact that it is going to show real operations, by real doctors, on real patients. Though the anonymity of the doctors is being preserved—for what that is worth in this publicity-seeking age—their colleagues may well think it is demeaning for doctors and nurses to appear as mummers on the television screen in order to provide entertainment for the great British public. The following are some of the subjects of the series: the treatment of cancer, an operation for mitral valvotomy, an operation on the

brain, and "a rare operation for short-circuiting the blood supplies to and from the liver as a result of cirrhosis." We hope that in their search for realism the B.B.C. will not find itself telecasting a death on the table. But even if it is not provided with this sensation the viewing public should be in for a real blood-curdling treat. When a group of medical and lay journalists saw an edited extract of a telecast of a mitral valvotomy, after attending a luncheon to launch the present programme, one or two of them (believed to be laymen) hovered on the verge of syncope, and one, it appears, not successfully.

The B.B.C. is determined to behave like the fat boy in *Pickwick* and to pop round the corner into people's homes via the television set in order to make their flesh creep. It will probably succeed, but many doctors will have little doubt that the effect will be to heighten people's anxiety about the state of their own bodies and their own health and increase the hypochondria and neurosis which are all too prevalent in so-called civilized societies to-day. When the B.B.C. televised a series under the title *The Hurt Mind*, a very large number of persons, we were given to understand, as a result got into touch with their own doctors asking whether they could have electric shock treatment. It may be doubted whether those organizing the programme thought this a desirable result, and whether those responsible for the present programme have really thought of the effect on people's minds of witnessing on the television screen something which, though familiar enough to the medical men taking part in the present series, is full of mystery, foreboding, and fearfulness to the mind of the ordinary person. The televiewer will no doubt go through all the discomforting reactions of the medical student who believes he is suffering from the diseases he is reading about. Given a basic ignorance of the simplest facts of biology the uninstructed layman is unlikely to be less mystified than before when he witnesses the operation on the patient with the cirrhotic liver. And if the B.B.C. takes its cameras into operating theatres, however respectably, where is the press photographer going to learn his manners? The Chief Executive, B.E.A., in a letter to *The Times* on Monday describes the recent intrusion of cameramen into the Munich hospital "in order to photograph an unconscious man [i.e., Mr. Busby] lying in a critical condition in an oxygen tent." In reply to his protest at this invasion of the hospital by 20 press photographers, the German doctor "politely indicated that they were my countrymen"—in fact, ordinary Britons behaving uncommonly like the B.B.C.

This pandering to the prevalent interest in the morbid goes against all the efforts many people and organizations have made over the years to interest the public in health rather than in disease. Those responsible for health education know how difficult it is to try to persuade people to think in terms of health rather than of disease, and, for the most part, have refused to take the easy way by feeding the curiosity of the layman about matters which he can at the best most imperfectly understand. A medical editor from the U.S.A. speaking in a symposium on medicine and the press at the meeting of the World Medical Association in Istanbul last October referred with approval to the fact that "the former so-called doctor books that attempted to tell the layman how to treat almost any disease fortunately have been replaced by health books which stress the hygiene of living and deal with disease from the standpoint of prevention." If the B.B.C. tackled problems of health on these lines it might earn the gratitude of the medical profession. By dramatizing disease they are looking back instead of forward.

[1] *Daily Telegraph*, February 5.

ELECTROENCEPHALOGRAPHY

Several clinical specialties have benefited from the information provided by electroencephalography, the diagnostic uses of which Sir Russell Brain defines in his Frederick Price lecture, printed in the opening pages of this issue. Unfortunately the state of electroencephalography in Britain to-day is unsatisfactory, for reasons which we explained 18 months ago.[1] A special committee of the Royal College of Physicians, under the chairmanship of Sir Russell Brain, has now issued a report[2] on this matter and made recommendations for improving the quality of the work done in clinical electroencephalography. Commenting on the present defects, the committee states: "In our view the whole sorry story we have presented begins with failure to interest neurologists and psychiatrists, and recruit . . . clinical registrars into this subspecialty of the neurological sciences."

There are a few large E.E.G. departments in the postgraduate teaching centres which do the bulk of teaching and much of the research in this field. Most of the undergraduate teaching hospitals have departments, but the majority of E.E.G. units are small ones situated mainly in mental hospitals. Even in the postgraduate centres the recruiting of junior staff is almost impossible, while in the mental hospitals the medical direction of units may be non-existent, merely titular, or undertaken by partly trained and overworked clinicians. The failure to interest registrars suitably trained in neurology and psychiatry in further training is largely due to the absence of any worthwhile career in electroencephalography. The committee recommends that for the present "the training period for a selected trained neurologist or psychiatrist, who is entering the field with the intention of taking charge of an E.E.G. department, should be not less than one year of full-time study." Three or four training posts of registrar or senior registrar grade at the Institutes of Neurology and of

[1] Leading article, *Brit. med. J.*, 1956, **1**, 1412.
[2] Royal College of Physicians of London. Committee on Electroencephalography, Revised Report, January, 1958.

Psychiatry would probably meet immediate needs, but consideration should be given to establishing a further postgraduate training centre in the north. The committee believes that to equip men of the highest calibre for entry into this field a minimum of two years' training would be necessary, and that the instruction given in research methods in neurophysiology would be of such a standard to enable the student to take a Ph.D. degree. In order to make this effort worth while subsequent careers in electroencephalography must be made more attractive. E.E.G. departments should be headed by clinicians of consultant status able to spend at least half and preferably two-thirds of their time in the practice of the subject. This does not mean that all this time is spent reporting on E.E.G. records; the head of the department should undertake or supervise special investigations in electroencephalography or related neurophysiological fields. The day is past when electroencephalography consisted of routine records performed in only one way by a technician at one time of the day and reported on later by a busy clinician. For the rest of his time the head of the department would work in his own specialty, as, for instance, a neurologist, psychiatrist, or paediatrician. The committee also examined the unsatisfactory position of the numerous small isolated E.E.G. units and suggested that some of them could be grouped together under one or two consultants. The consultants could visit the outlying units regularly if this were easier than making the patients travel long distances. The consultant ought also to have access to a few beds for special E.E.G. investigations, such as, in the words of the report, "sleep records, sphenoidal electroencephalography, activation under convulsant drugs, and localization of epileptogenic foci."

These sensible proposals would do much to improve the quality of work in electroencephalography. It remains now for boards of governors and regional hospital boards to provide the working conditions which will induce registrars not only to take the extra training but also to stay in the field. They must also be prepared to allow registrars the year's leave necessary to take the training. It is extraordinary how much easier it is to persuade a committee to spend £1,500 buying an E.E.G. machine than the same sum on equipping the man needed to make use of that machine. As Sir Russell Brain said in his lecture, "Electroencephalography is of value only when the clinician knows what question to put to the machine, and how to interpret the answer it gives."

The committee, by its terms of reference, concentrated largely on clinical electroencephalography and made little reference to its relation with the basic sciences. Clearly a clinical department needs to be headed by a medical man of consultant rank, but in many places, especially the United States, many of the best E.E.G. departments, and the most original research, are directed by graduates in physiology or psychology rather than in medicine. If electroencephalography is to continue advancing in Britain as it is in other countries, some university departments of physiology should be ready to foster active interest in it. Very distinguished contributions to basic neurophysiology are still being made in Britain, but mainly in fields remote from E.E.G. There is a case to be made for setting up a committee, parallel to that of the Royal College of Physicians, of interested university and Medical Research Council workers to consider how to encourage the applications of E.E.G in neurophysiology.

THE "BURR" CELL IN URAEMIA

Normal red blood cells in man are circular biconcave disks. When the cells have an irregular shape they are called poikilocytes, and the commonest form is the pear-shaped cell often found in states of anaemia. In 1949 S. O. Schwartz and S. A. Motto[1] described a particular form of poikilocyte which is of normal size but has projections which may be up to half the diameter of the cell in length. The cells are reminiscent of the burrs from a burdock plant, and Schwartz and Motto named them "burr cells." These burr cells were said to occur particularly in cases of uraemia, carcinoma of the stomach, and bleeding peptic ulcer, though they might be seen occasionally in other diseases. They were not found in any specimen taken from 100 normal subjects. Similar cells were described in the case of a girl aged 18 born of parents who were first cousins and who suffered from retinitis pigmentosa together with a diffuse disease of the central nervous system resembling Friedreich's ataxia.[2] J. V. Dacie[3] states that uraemic patients with anaemia frequently have contracted and deformed erythrocytes, and that an almost triangular cell is the characteristic type, though one of his illustrations shows characteristic burr cells. He regards these deformed cells as one of the components of a haemolytic anaemia accompanying progressive renal failure.

The subject has recently been re-examined by W. A. Aherne[4] in an attempt to assess the clinical significance of burr cells, especially in states of azotaemia. He describes in detail five patients showing the phenomenon. The first two cases were middle-aged men with progressive renal failure leading to death, which is the characteristic set of circumstances in which burr cells are found. Case 3 was a girl aged 10 years with reversible renal failure, and Case 4 was a baby also with anaemia and reversible renal failure. These two cases in childhood were possibly examples of a syndrome described by C. Gasser and his colleagues[5] in which a severe haemolytic anaemia is associated with bizarre poikilocytes resembling burr cells. Aherne also made observations on 25 other azotaemic patients and found that burr cells usually do not appear in significant numbers until the blood urea is higher than 175 mg. per 100 ml. Moreover, serial studies showed that burr cells were much more likely to appear in those patients in whom the blood urea was rising steadily than in those in whom it was fluctuating. This fact was related to the finding that burr cells were frequently associated with a fatal termination to the illness. In brief, therefore, the occurrence of appreciable numbers of burr cells in a patient with a raised level of blood urea should be regarded as

[1] Schwartz, S. O., and Motto, S. A., *Amer. J. med. Sci.*, 1949, **218**, 563.
[2] Bassen, F. A., and Kornzweig, A. L., *Blood*, 1950, **5**, 381.
[3] Dacie, J. V., *The Haemolytic Anaemias*, London, 1954.
[4] Aherne, W. A., *J. clin. Path.*, 1957, **10**, 252.
[5] Gasser, C., Gautier, E. Steck, A., Siebenmann, R. E., and Oechslin, R., *Schweiz. med. Wschr.*, 1955, **85**, 905.

a grave prognostic sign, even though it does not inevitably spell death. In childhood, cells of similar appearance, though probably of different origin, may appear in acute haemolytic anaemia, which may respond to energetic blood transfusion.

Aherne suggests that burr cells may arise from an acceleration of the normal processes of degradation of the red cells. The accompanying anaemia may be largely due to their phagocytosis by the reticulo-endothelial system, and it may be significant that deformed red cells, not unlike burr cells, may be found in patients who have undergone splenectomy for any reason.

ALBOMYCIN AND GRISEIN

The first account of a new Russian antibiotic, albomycin, in the English language was a paper by G. F. Gause[1] in this *Journal*. Very remarkable properties were claimed for this substance, including an activity against staphylococci ten times more powerful than that of penicillin. Some of the properties of a sample of albomycin obtained in Britain with difficulty were described by L. P. Garrod and Pamela M. Waterworth,[2] who confirmed that it had a high but oddly selective activity against salmonellas and other intestinal bacteria and against some of the Gram-positive cocci. They failed entirely to confirm the action claimed against staphylococci: on the contrary they found that these organisms apparently became enormously resistant to albomycin, even during overnight incubation. Because of doubts about the purity of the sample used for this investigation, further tests were carried out on an ampoule of pure material. Apart from its greater activity, this sample behaved in the same way, bacterial resistance to it developing with unexampled rapidity.[3]

A specimen of albomycin recently reached the United States, where it was examined by E. O. Stapley and R. E. Ormond,[4] whose report on it is discussed in an accompanying paper by S. A. Waksman.[5] These authors have shown that albomycin is closely related to if not identical with grisein. Both are amorphous red substances containing iron and amino-acids, and both are separable into four active constituents. Their chemical and physical properties are as nearly indistinguishable as would be expected of two samples of the same substance having different degrees of purity: their antibacterial spectrum is the same, and organisms resistant to each are also resistant to the other. Grisein was discovered by Waksman and his colleagues eleven years ago. Perhaps the best description of it is that given by D. M. Reynolds and S. A. Waksman,[6] who regarded it as unlikely to be of therapeutic use owing to the rapidity with which bacterial resistance to it develops, but suggested that its use in combination with streptomycin might to some extent overcome this drawback. Since nothing further has been heard of this suggestion, it may be assumed that the American discoverers of grisein finally abandoned it as a useless curiosity.

Waksman's paper is entitled "Penalty of Isolationism," and he deplores "the frequently unjustified creation of 'new species' of antibiotic-producing organisms and of 'new antibiotics,'" observing that these difficulties "can be avoided only by close collaboration among the scientific workers throughout the world." It is remarkable that a statement on similar lines should have been issued from Moscow at nearly the same time. N. A. Krassilnikoff,[7] of the Institute of Microbiology, Moscow, complains that "most authors, in describing antibiotics which they have discovered, give either no information or insufficient information about the actinomycetes which produce them." He goes on to discuss the taxonomic position of *Actinomyces griseus*, and claims that among the first 500 of 5,000 strains of this organism in his possession 15 different species have been identified. A method which he commends for establishing identity or otherwise among actinomycetes is the observation of mutual antagonism. This is to assume that all such organisms are sensitive to an antibiotic formed by a different species, and also presumably that different species never form the same antibiotic. There being 23 species of *Penicillium* and 7 of *Aspergillus* which form penicillin, the second assumption is certainly not generally true. There are only a few authorities in the world who are at home in the difficult subject of classifying these numerous organisms, and it should be left to them to find the way through this complicated maze.

INDICATORS OF CHRONIC IRRADIATION

The rapidly expanding atomic energy industry and the widespread use of radioactive isotopes are greatly increasing the size of population frequently exposed to ionizing radiation. The experiences of the pioneer radiologists and radiographers make it imperative that the health of this new and growing population of workers should be adequately protected. Normally two methods of control are used concurrently. These are, first, the physical measurement by monitoring instruments of the dose received by each individual, which entails his active co-operation, and secondly the time-honoured routine blood count.

Apart from the genetic response of the generative tissue to irradiation, the response of the haemopoietic system is the most sensitive among the mammalian tissues. Consequently it has long been believed that haematological changes would be an early indication of radiation damage. Recently doubt has been thrown on the value of routine blood counts to show the damage, it being held that they are insensitive indicators of both acute and chronic irradiation and may not mirror the damage to the bone marrow.[1,2] But M. Helde,[3] by making repeated total white cell counts and comparing the results with the expected normal distribution, was able to distinguish between individuals who were in contact with radiation and those who were not. Now P. W. Edmondson reports an experimental approach to the problem in this *Journal* (p. 363). He has

[1] Gause, G. F., *Brit. med. J.*, 1955, **2**, 1177.
[2] Garrod, L. P., and Waterworth, P. M., ibid., 1956, **2**, 61.
[3] —— ibid., 1956, **2**, 1362.
[4] Stapley, E. O., and Ormond, R. E., *Science*, 1957, **125**, 587.
[5] Waksman, S. A., ibid., 1957, **125**, 585.
[6] Reynolds, D. M., and Waksman, S. A., *J. Bact.*, 1948, **55**, 739.
[7] Krassilnikoff, N. A., *Ann. Inst. Pasteur*, 1957, **92**, 597.

used guinea-pigs, which as a species are known to be very sensitive to daily irradiation,[4] but in addition to examining the peripheral blood he has performed serial examinations of bone marrow. A fall in the total white cell count was noted fairly soon after the beginning of the experiment, and eventually a severe neutropenia developed. These changes contributed little to the killing effects of the irradiation, since it was a thrombocytopenia, giving rise to widespread haemorrhages and terminal anaemia, which eventually killed the animals. The bone marrow gave no reliable indication of damage until the terminal stages, when in response to the anaemia it became almost completely erythropoietic.

Edmondson's animals received a far higher dose—namely, 10 r of gamma rays per day—than would be allowed as an occupational exposure, and, as the daily dose extended over a 16-hour period, repair was likely to be affected by the next day's irradiation. Despite these differences from human hazards, his results are of considerable interest. After single large doses of radiation the red cell precursors are usually considered to be more sensitive than the myeloid series.[5-7] Edmondson's finding that sensitivities are reversed with chronic irradiation may be due to a greater power of recovery in the erythropoietic series; and his observation of the bone marrow's response to the loss of red cells in spite of a mean accumulated dose of 1,780 r indicates a remarkable resilience in a series of otherwise very radiosensitive cells.

The guinea-pig in common with man and the dog is prone to widespread haemorrhages after a single large dose of radiation. The most important factor in this haemorrhagic tendency is believed by A. C. Upton[8] to be a thrombocytopenia, and more recently B. Lindell and J. Zajicek[9] have shown that even in the rat, which is not particularly prone to post-irradiation haemorrhage, the megakaryocytes are reduced to 20% of their normal numbers after a dose of 250 r of *x* rays. Edmondson has also found both a thrombocytopenia and a reduction in megakaryocytes in his chronically irradiated animals. These findings might at first suggest that routine platelet counts by one of the more reliable methods could be of value in radiation control. The pattern of the platelet response, however, is not straightforward. Edmondson found the initial fall was followed by a return to near normal values, and only later did a permanent fall occur. A biphasic response of a similar nature has been observed among those Marshall Islanders who received a large dose of radiation from thermonuclear fall-out.[10] Only when this response is understood better will it be worth while considering the suitability of platelet counts in the control of chronic irradiation.

[1] Mole, R. H., *J. clin. Path.*, 1954, **7**, 267.
[2] Loutit, J. F., *Brit. J. Radiol.*, 1955, **28**, 647.
[3] Helde, M., in *Advances in Radiobiology*, 1957, p. 361, Edinburgh.
[4] Lorenz, E., Jacobson, L. O., Heston, W. E., Shimkin, M., Eschenbrenner, A. B., and Deringer, M. K., in *Biological Effects of External X and Gamma Radiation*, 1954, 24, New York, Toronto, London.
[5] Bloom, M. A., in *Histopathology of Irradiation from External and Internal Sources*, 1948, 162, New York, Toronto, London.
[6] Rosenthal, R. L., Pickering, B. I., and Goldschmidt, L., *Blood*, 1951, **6**, 600.
[7] Hulse, E. V., *Brit. J. Haemat.*, 1957, **3**, 348.
[8] Upton, A. C., *Blood*, 1955, **10**, 1156.
[9] Lindell, B., and Zajicek, J., in *Advances in Radiobiology*, 1957, p. 376, Edinburgh.
[10] Cronkite, E. P., Bond, V. P., and Durham, C. L., in *Some Effects of Ionizing Radiation on Human Beings*, 1956, Washington.

THE BABY'S SWALLOW

In recent years the work of H. Waller[1] has added much to our knowledge of the mechanism of an infant's sucking, the causes of failure of breast feeding, and how to remedy them. K. C. Richardson[2] has shown that in breast feeding there is a *vis a tergo* supplied by the contractile myoepithelial cells which surround the alveoli and extend down the walls of the ducts; this force renders the infant's task much easier. In artificial feeding, gravity has to replace this force; hence the importance of holding the bottle correctly tilted.

Happily the problems for infants who have to be artificially fed have largely been solved by the general adoption of dried milk feeds, but there still remain a large number of "difficult feeders" in whom the trouble lies not in the choice of food or in organic disease but in the processes of sucking and swallowing. These infants, with failure to thrive, swallowing of air, vomiting, slow feeding, and similar difficulties, continue to provide daily problems in the lives of many practitioners. If the infant is normal and the feeds offered are adequate in constituency, volume, and total daily intake, and yet the infant presents with any of these problems, there remain the bottle and the teat to consider. There is still some argument about the most suitable shape of bottle, though most authorities are agreed on the superiority of the straight variety over the boat-shaped. Less attention has been paid to the teat, but, as a result of their cineradiographic studies, G. M. Ardran, F. H. Kemp, and J. Lind[3] believe that this is an important factor. The teat should, they consider, be of soft consistency—not rigid—for this softness allows a teatful of milk to be swallowed with each jaw and tongue movement, whereas with a rigid teat three or four such movements may be necessary; and there should be an air inlet, since this lessens the amount of air ingested during feeding. The neck should be narrow (approximating to the diameter of the base of a mother's erect nipple) and the hole should be large enough to permit a fast drip. A healthy infant will then probably take his required feed in ten minutes or less with complete safety and less air-swallowing.

A further interesting finding in the study of Ardran and his colleagues concerns the significance of the tonsils and pharyngeal lymphoid tissue in swallowing. They show that these act as space fillers and prevent milk from reaching the posterior pharyngeal wall, thus assisting in keeping the airway open and directing some of the milk into the lower pharynx. When a sufficient quantity has accumulated there, the airway is closed and the infant swallows, the bolus being helped down the oesophagus by a peristaltic wave. As soon as the bolus is passed, the airway is restored.

We record with great regret the death on February 11 of Dr. Ernest Jones, friend and biographer of Sigmund Freud, and consulting physician to the London Clinic for Psycho-Analysis.

[1] Waller, H., in Sir E. Holland's *British Obstetrical Practice*, 1955, Chapter 7, Heinemann, London.
[2] Richardson, K. C., *Proc. roy. Soc. B*, 1949, **136**, 30.
[3] Ardran, G. M., Kemp, F. H., and Lind, J., *Brit. J. Radiol.*, 1958, **31**, 11.

A CASE OF HEALTH

BY

RICHARD ASHER, M.D., F.R.C.P.

Physician, Central Middlesex Hospital, London

Many cases of unusual illness are described in these columns, so it may make a change if I report a case of unusual health. The lady I describe here is healthy not only in the sense of never being ill but in the more practical fashion of being useful and hard at work for 76 consecutive years with only 10 days' illness. My knowledge of her is purely social; she never consults doctors: "I don't believe in them," she says.

Fanny, as everyone calls her, was aged 90 on January 31 and works as a cook and general servant at a girls' day-school in London. She was born on January 31, 1868. She went to school till the age of 13, and then started work in domestic service. Since then she has worked at this profession without any illness or absence from work except for 10 days off in 1932 with bronchitis and severe fatigue after she had been nursing her husband with a fatal illness.

Fanny at her oven, cooking the puddings.

She started her present post 42 years ago; it is both strenuous and responsible. She cooks for 90 people and is also housekeeper to the headmistress. Her average working day is as follows: 6.30 a.m., gets up and takes her dog for a walk, after which she cooks breakfast for four. 9.30 a.m., goes out shopping for the school. 11 a.m., starts cooking the school lunch ready for 1 o'clock. 1.30 p.m., receives and sorts the dirty crockery brought down by the children, takes her dog for a walk, and then changes into a black dress and apron for the afternoon. From 2 to 4 p.m. she is on duty for the front-door bell, but manages to get a little rest during this time. 4 p.m., gets tea ready for the staff of seven teachers. 4.30 p.m., clears up tea. 7 p.m., prepares supper for her mistress. 9.30 to 10 p.m., takes her dog out for an evening walk and then goes to bed.

On Saturdays she does cleaning and polishing. On Sundays she does her washing in the morning and then cooks and serves lunch. She takes the afternoon off and prepares a cold supper for the evening. She stays at the school during the holidays even when her mistress is away, when she is quite alone in the house. She is an alert, spry little woman who moves quickly and vigorously. She enjoys her work, and her mistress, who is devoted to her, regards her as a treasure.

Though many people are very active at 90, it is rather unusual to perform quite so much responsible work at this age and to work at one job so many years without absence through illness. This rare condition of health is probably hereditary—her mother lived to 100, her sisters died at 89 and 86, and her brother is 86.

ORDER OF ST. JOHN OF JERUSALEM

Those recently appointed to, or promoted in, the Venerable Order of the Hospital of St. John of Jerusalem include the following members of the medical profession:

As Knights: Drs. J. T. Whitley and R. V. S. Cooper, *As Commanders (Brothers):* Sir Charles Dodds, F.R.S., Air Vice-Marshal L. M. Corbet, Messrs. D. P. McIntyre and D. W. Montgomery, and Drs. J. C. R. Buchanan, C. H. Drake, M. Y. Paget, G. Swapp, and H. H. Hurst. *As Officers (Brothers):* Squadron Leader P. Cauthery, Mr. S. W. Cooper, and Drs. H. D. Teare, Chia Boon Leong, W. Duncan, C. T. Newnham, A. Morrison, A. Chalmers, C. F. Fairlie, T.D., A. G. Walker, R. G. Sprenger, R. H. Kipping, R. H. Scott, J. H. C. Clarke, G. N. M. Wishart, F. P. Wallis, S. G. Nelson, J. M. Pedler, N. G. Hoddle, and M. F. Leslie. *As Associate Officer (Brother):* Dr. N. Pines. *As Officer (Sister):* Dr. Florence E. Stewart. *As Serving Brothers:* Major K. C. Greenwood, The Reverend R. H. Smallwood (Assistant-Chaplain), and Drs. J. F. J. Kelly, F. N. Grannum, A. C. Kirton, H. W. Morck, E. M. Sharples, W. B. R. Jones, W. Nixon, Wong Wa Kwan, Lam Yu Shing, Woo Pak Foo, Lam Chiu Chun, W. A. R. Mailer, E. W. Tapley, R. F. Mackenzie, R. W. Rutter, W. H. Mylechreest, D. D. Towle, J. A. Wilson, T. S. McKean, K. E. Inman, J. T. Cullen, A. W. Burton, J. D. Fotheringham, F. L. Thyer, and W. J. Nicholl. *As Associate Serving Brothers:* Drs. I. S. Patel, S. Lurie, and H. M. Khas. *As Serving Sisters:* Drs. Kathleen E. Thompson and Annie D. Gibson.

Reports of Societies

OBSTRUCTION OF THE SMALL INTESTINE

[FROM A SPECIAL CORRESPONDENT]

On February 5 the Surgical Section of the Royal Society of Medicine discussed "Small-bowel Obstruction." Mr. A. DICKSON WRIGHT, the Section President, was in the chair.

Acute Obstruction

Mr. R. V. COOKE, the opening speaker, dealing with acute obstruction, began by quoting the Registrar-General's mortality figures. The death rate for acute obstruction had dropped from 4,000 per annum in the decade before the second world war to just under 3,000 at the present time. This was no very dramatic improvement, and part of it might be accounted for by improved anaesthesia, intravenous infusion, and the services of the chemical pathologist. Obstruction of the small intestine was a treacherous condition. The average general practitioner saw only two cases a year, yet it was vital that he should make the diagnosis early and send these patients to hospital forthwith. A fatal issue might follow the delay when the initial signs were missed or the case was thought to be "only an early one." Delay was the great killer in this disease, whether in the home or in hospital. Mr. Cooke expressed his "violent antipathy" to three common causes of delay in hospital. Some thought, he said, that they could differentiate accurately between simple obstruction and strangulation; this attitude could result in unjustifiably conservative treatment with tragic consequences. Mr. Cooke thought it impossible to distinguish between these two types of obstruction, and he described some alarming cases to illustrate this point. Another cause of delay was the use of the Miller–Abbott tube; a great deal of time might be needed to introduce it into the small bowel, and even if the manœuvre was successful the tube's value in acute obstruction was very limited. A third cause of delay was the policy of "suck and drip to death": pre-operative transfusion should be rapid and aimed at getting the patient into a state suitable for operation at the earliest possible opportunity.

Mr. Cooke then analysed replies from registrars throughout the country to a letter written asking a number of questions on acute obstruction. Nearly all agreed with him that it was impossible to make a certain diagnosis between simple and strangulating obstruction, and some thought it useless and dangerous to try to do so. In patients who were

not dehydrated immediate operation was generally advised. If there was fluid and electrolyte depletion, rapid pre-operative intravenous infusion was of great value, whole blood being particularly beneficial. If the bowel was strangulated, the patient would deteriorate despite intensive infusion, and only early operation would improve his condition. Delay was justified only in the patient whose abdomen was a battlefield of scars and who had little peritoneal cavity left, but even in these cases conservatism could be overdone. Radiography helped in making a diagnosis, although sometimes it was inconclusive. Obstruction after elective abdominal surgery should always be treated by immediate operation; the patient could withstand the second procedure well. But obstruction occurring almost immediately after operation was particularly hard to diagnose.

At operation the distended bowel should be decompressed by means of a needle or in some other way: the abdomen would then be easier to close, post-operative discomfort lessened, and recovery hastened. Removal of the toxic fluid in the dilated gut would also prevent it from exerting a systemic effect.

Mesenteric infarction was being met with increasingly, and both its diagnosis and its treatment were difficult. Occasionally "mesenteric angina" was diagnosed in a patient complaining of pain after meals. An aortogram might then reveal constriction of the superior mesenteric artery. Endarterectomy or arterial grafting might perhaps prevent mesenteric infarction in such cases. Mr. Cooke's final word of advice was, "Don't be too clever."

Chronic Obstruction

Professor JOHN BRUCE, P.R.C.S.Ed., then spoke on chronic obstruction of the small intestine. The means of diagnosis in this part of the gut were feeble, so that lesions of the small bowel were usually diagnosed only when they had caused nearly complete obstruction. The small bowel had two functions, absorption and transport, and pathological lesions interfered with both. Partial obstruction caused colicky pain, made worse by meals, noisy intestinal sounds, visible peristalsis and palpable thickening of the gut. Diarrhoea was not uncommon when the obstruction was almost total. Deficient absorption, associated for instance with regional ileitis, might cause a megaloblastic anaemia due to vitamin-B_{12} deficiency; this was particularly likely in high jejunal obstruction. Small-bowel disease should always be suspected in the presence of the triad intestinal colic, megaloblastic anaemia, and normal gastric acidity. A similar megaloblastic anaemia was sometimes caused by the presence of a blind loop of small bowel which had been by-passed surgically; bacteria in the loop multiplied and competed with the body for vitamin B_{12}. Administration of the vitamin, or sterilization of the gut with antibiotics, would temporarily relieve this anaemia. After extensive resection of small bowel a microcytic anaemia occurred owing to iron deficiency; protein, calcium, and other deficiencies were also found.

Professor Bruce then discussed some interesting causes of chronic small-bowel obstruction. A low-grade peritonitis, such as that due to appendicitis, especially if smothered by antibiotic therapy, might result in extensive adhesions. If obstruction from this cause was not relieved by conservative means it might be necessary to perform a side-to-side anastomosis between the small bowel and the transverse colon; the fistula thus created would close as soon as bowel function returned to normal. The cause of adhesions was unknown; in animal experiments it had been shown that covering bare areas of the abdominal wall did not prevent their formation. The administration of cortisone before and after operation would, however, prevent adhesions in animals. In patients with very extensive peritoneal adhesions Noble's operation, which consisted in suturing the loops of small bowel together in an orderly fashion so that they did not kink, had been proved to be effective.

Allergic oedema might cause obstruction, and simple spasm was another infrequent cause of temporary occlusion. Benign and malignant neoplasms of the small gut, though rare, were seen from time to time. Leiomyomata of the bowel wall had a tendency to necrose, sometimes with massive haemorrhage. Carcinoid tumours might be solitary or multiple and sometimes had a hereditary basis; at the time of operation 60% would have already metastasized. They grew very slowly and should be excised radically.

Discussion

In the ensuing discussion Mr. P. T. SAVAGE described his own series of 115 cases of small-bowel obstruction (excluding external hernia). There were 17 deaths, but in those under 70 years of age the mortality was only 7%; in those over 70 it was 34%. While stressing the value of radiography in diagnosis, he warned that it might occasionally mislead. Decompression of the gut at operation was very valuable, and Mr. Savage demonstrated his own instrument for this purpose. Professor H. W. RODGERS showed *x*-ray films of a patient in whom fluid levels had persisted for a month after operation despite a good appetite and normal bowel movements. Several such cases had been seen.

Sir RALPH MARNHAM voiced suspicion about the value of radiographs in diagnosis and cautioned against relying too much on them. Mr. RODNEY SMITH thought radiography of value, but that it needed as much judgment in interpretation as did physical examination, of which it was really an extension. He defended the Miller–Abbott tube as being useful in a very limited number of cases, particularly those with diffuse plastic adhesions.

Mr. DICKSON WRIGHT made a few closing remarks. He emphasized the importance of the severity of the initial pain as a guide to the seriousness of the case. The contents of obstructed bowel were not toxic, and all fluid aspirated from the stomach should be returned to the patient in a rectal drip. Perhaps some of the value of *x*-ray examination lay in the short delay it caused, thereby allowing time for a more thoughtful assessment of the case.

Preparations and Appliances

ALVEOLAR CARBON DIOXIDE ANALYSER

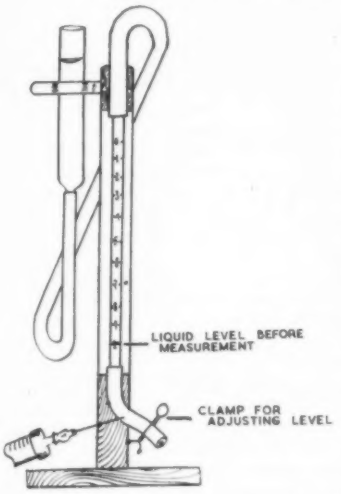
Mr. L. R. C. HAWARD, senior clinical psychologist, Winterton Hospital, Sedgefield, Stockton-on-Tees, writes: An accurate estimation of changes in the percentage of alveolar CO_2 is not infrequently required in both clinical and research work. Among obvious examples two may be cited: the alveolar content change in diabetes mellitus due to stimulation of the respiratory centre (following the haematological take-up of excess acids) and the determination of the exact degree of hyperpnoea following hyperventilation for electroencephalographic purposes.

As a diagnostic instrument in the laboratory, clinic, or surgery the classical Haldane–Priestley apparatus has many disadvantages, and modern techniques, using modifications of the original instrument, have been made by many investigators. Probably the two most effective types of apparatus in use to-day, which have much in common, are those introduced by Scholander (1942) and Asmussen and Buchthal (1949). I have redesigned Scholander's "quick analyser" to obviate certain difficulties inherent in the original design, and the cost of the instrument has been greatly reduced.

In its new form the apparatus consists of a wooden burette stand to which is affixed a 1-ml. pipette graduated in 0.01-ml. intervals and connected by stethoscopic tubing to a 25-ml. glass reservoir. The latter is held in place by a Terry spring clip which allows the "head pressure" of the liquid to be adjusted, and between the pipette and the vertical column of the stand a strip of white cardboard is positioned in order to make the meniscus easy to see. The lower end of the pipette is closed by another length of stethoscopic tubing and a spring clamp. The burette clamp is preferable to the Sterivac screw clamp, since the former permits a more delicate control over the meniscus position.

The reservoir is filled with a 10% solution of potassium hydroxide to which a few drops of caprylic (*sec.* octyl) alcohol have been added to stabilize aeration. By operation of the clamp the liquid will flow *down* into the pipette. After allowing time for the atmospheric CO_2 present in the pipette to be absorbed, the meniscus should gradually be lowered to the 1-ml. mark; this is best done by holding a finger-tip over the end of the tube and so controlling the release of the air by both finger and clamp.

The "end-expiratory sample" should be obtained by the usual methods, with careful attention to the safeguards detailed elsewhere (Haward, 1955). Briefly, the patient expels air as completely as possible through a rubber tube of small bore. In my department the tubing is attached to a No. 4 B.O.C. face-mask, which the patients find more comfortable in use. When expiration has been as complete as possible, a 2-ml. syringe is connected to the hypodermic needle already inserted in the tube as close to the patient's mouth as possible, and a little over 1 ml. of residual air is withdrawn. The syringe complete with needle is now removed and the needle embedded in a rubber cork to seal the contents while they are allowed to cool to ambient temperature. The rubber bung is then removed and the sample reduced to 1 ml. by expelling the surplus air; in order to have an accurate and consistent volume it is desirable to use a piece of wood as a key between the syringe head and the plunger thumb-piece—the plunger can then be quickly depressed until it touches the key, and the contents can then be injected into the lower piece of tubing of the analyser.



The meniscus will be seen to rise to the top of the pipette, and will come to rest at some distance below the zero mark according to the volume of CO_2 which has been absorbed. The meniscus will now give a direct reading of the CO_2 content per ml. of the respiratory sample, and it has been found possible to measure to within 2 microlitres with reasonable accuracy—that is, 0.2% of the sample.

The advantages of this type of apparatus all lie in the fact that the gaseous contents of the syringe are not injected into a liquid; this immediately eliminates those troublesome sources of error which arise from foaming of the liquid, drainage time, and the adhesion of bubbles to the walls of the tube. Frequent piercing of the rubber tube will eventually cause leakage, but this has been quite negligible in my department. Vogt Lorentzen (1953) has devised an ingenious way of overcoming this by using a curved cannula attached to the syringe, but it seems much simpler to change the rubber tubing after a certain number of punctures have been made. The use of stethoscopic tubing is stressed because its dimensions (5 mm. bore and 12 mm. external diameter) will delay the onset of leakage to a considerable degree.

I am indebted to Dr. Harald Erikson, of the Institute of Respiratory Physiology, Oslo University, for his helpful criticism and invaluable advice.

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Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Carcinoma of the Breast

SIR,—In your leading article on carcinoma of the breast (*Journal*, February 1, p. 269) the problems related to pregnancy in a patient who has undergone a radical mastectomy for cancer are briefly discussed. Your leader-writer observes that "ideally, for such women to become pregnant is imprudent"; and thereafter goes on to discuss the circumstances when an unwanted pregnancy may be terminated, concluding that "its early termination if it has occurred is a wise course." I find this too dogmatic. While I have no ethical objections whatever to the operation of therapeutic abortion, I am reluctant to have my decision prejudged in respect of the individual patient. I do not suppose that your leader-writer means to imply that a decision to allow an unwanted pregnancy to continue is necessarily an unwise course; but already an impression to that effect is widespread among certain practitioners, and is communicated to the patient and her relatives before she is seen by the gynaecologist. This, at least, is imprudent.—I am, etc.,

Manchester, 13. W. I. C. MORRIS.

Stiff-man Syndrome

SIR,—I cannot give Dr. Richard Asher's article (*Journal*, February 1, p. 265) greater praise than to say that I read it before the newspaper at breakfast. It was almost as good as attending the meeting at the Central Middlesex would have been. Not all medical subjects are suitable for this kind of writing, but single cases of great interest are, I think, best described in this very readable way. How dull (and unread) Dr. Asher's story could have been.—I am, etc.,

Enfield, Middlesex. C. ALLAN BIRCH.

SIR,—The great rarity of the syndrome so clearly described by Dr. Richard Asher under the title "A Woman with the Stiff-man Syndrome" (*Journal*, February 1, p. 265) is manifest by the syndrome having escaped the attention of Charcot and his followers at the Salpétrière school at Paris. I would like to make only one suggestion—namely, that minor cases of the same kind may have sometimes been labelled as cases of extreme tenderness of uncertain nature. Following Charcot round the wards on one occasion I remember the case of a youngish woman, said to be an example of extreme tenderness of the skin, of uncertain nature. Of course she was not meant to be examined by the students and young doctors accompanying Charcot. I only want to suggest that some cases of extreme tenderness, or sensitiveness to touch, may really have been minor examples of the syndrome so admirably described by Dr. Asher and the American physicians of the Mayo Clinic. Clinical biopsies were not always made in those days in search of the microscopical signs of a true myopathy.—I am, etc.,

London, N.W.1. F. PARKES WEBER.

SIR,—I was most interested to read Dr. Richard Asher's article on this subject (*Journal*, February 1, p. 265), particularly as I have recently seen a man whom I believe to suffer from this condition. He has visited several hospitals in the London region and may be well known to some of your readers.

Mr. L. L., aet. 35, states that he had tetanus two years ago and since then has had episodes of painful cramps in the arms and legs which may last from two hours to several days. Associated with this he sometimes has retention of urine. When I saw him in December, 1957, I did electromyograms on the affected muscles and found no evidence of myotonia or irritative discharges. The motor unit pattern was of normal appearance and in no way resembled a myopathy. The extraordinary feature was that,

although the muscles remained hard and bunched-up and the corresponding joint almost immovable, the electrical activity was inconstant and at times was entirely absent (co-axial needle electrodes were used).

Physiological literature contains many references to methods of producing contracture (reversible shortening of muscle without electrical activity),[1] and it is interesting that one of the methods is injection of tetanus toxin in the cat. McArdle[2] has described a somewhat similar case in a man who had an anomaly of muscle glycogen breakdown, and here also contracted muscles showed no electrical activity electromyographically. His patient responded well to dimercaprol (B.A.L.). Should Mr. L. L. present again elsewhere perhaps a trial of dimercaprol and a muscle biopsy would be worth considering. At present sedation is the only treatment of help, intravenous calcium gluconate being of no benefit.

I am grateful to Dr. E. R. Cullinan for permission to publish details of this case.

—I am, etc.,

London, E.C.1 E. D. R. CAMPBELL.

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[1] Gasser, H. S., *Physiol. Rev.*, 1930, **10**, 35.
[2] McArdle, B., *Clin. Sci.*, 1951, **10**, 13.

Industrial Dermatitis

SIR,—The papers by Dr. F. F. Hellier and Dr. H. R. Vickers on industrial dermatitis, published in your issue of January 25 (pp. 196 and 199), are extremely interesting and are valuable studies. Like Phillips's paper,[1] they present a gloomy picture of the prognosis in industrial dermatitis. One of the reasons for this is that they are all dealing with a selected group of patients—namely, workers whose skin trouble was sufficiently severe for them to be off work for more than three weeks and to claim industrial injury benefit. These cases represent only a fraction, and probably quite a small fraction, of the total number of men who developed dermatitis from industrial hazards.

In many instances, for each man whose dermatitis is severe enough to necessitate him being off work for more than three weeks, or being referred to a dermatologist at hospital, there may well be a dozen others who are not so severely affected and who are dealt with by the industrial medical officer or by their own practitioner and recover in a matter of days. The true facts only come to light when every case of dermatitis in the particular factory or industry is examined and analysed.

There is a real need for many more studies of the latter type to be carried out, and it can only be done by a joint team of industrial medical officers and dermatologists. When every case is examined, the prognosis is found to be not nearly so gloomy, but the overall incidence is considerably higher than the figures from dermatological clinics and Ministry of National Insurance offices indicate. Dr. Vickers and Dr. Hellier have shown that, in their selected material, factors other than the man's occupation are important in precipitating his industrial dermatitis. In most of the less severe cases the factors are inconspicuous or absent.—I am, etc.,

London, W.1. C. D. CALNAN.

REFERENCE

[1] Phillips, B., *Practitioner*, 1954, **172**, 531.

SIR,—In his interesting paper on the prognosis in industrial dermatitis (*Journal*, January 25, p. 196), Dr. F. F. Hellier produces evidence which supports many of one's impressions in dealing with this difficult subject. Essentially his figures suggest that approximately the same percentage of the subjects he investigated continued to have skin trouble whether they changed their jobs or not. This finding must surely encourage one to continue to be extremely hesitant about advising change of occupation in dermatoses thought to be industrial in origin. It is true he states that complete immunity from subsequent attacks is likely to occur only after a change of work, although the figures from his cases superficially would not seem to support this contention (i.e., 24% remaining clear while at their original work, and 25% remaining clear after changing their work). However, he does not indicate what proportion of those who changed work and had no further trouble were those who originally had sensitization reactions (as opposed to dermatitis from primary irritation). Reading between the figures, it would seem that most of this group did have such sensitization reactions, and with his inference that there is a better outlook for a man specifically sensitive one would not disagree. Indeed, where a specific sensitivity is involved, it is often possible, especially if an industrial medical officer can co-operate, to modify the job so that the responsible contact is excluded, and so allow the man to continue at his old work without the loss of earnings which all deplore.

For the subject with primary irritant eczema, or the eczema-prone individual, on the other hand, there is nothing to suggest that he will be free of further skin trouble in a different job, and it is questionable whether one's aim should be solely to try and achieve absolute freedom from rash. One does, however, agree with the statement that, "in most cases, every effort should be made to keep the man working at his old job with suitable precautions rather than advise him straightaway to change his work." The point might further be made that in patients with a non-sensitization dermatitis the doctor's encouragement to remain at the original work may go a long way towards obviating a man's emotional misery at having to undertake a less remunerative post unnecessarily, or, more, prevent him from brooding at home over a cutaneous misfortune which has stopped work altogether. These are both factors which would tend to aggravate badly the constitutional provocations of any eczema, making the last state worse than the first, and are to be avoided if possible on those grounds. A disinclination to advise a change of work, unless impressed by a convincing exhibition of specific sensitivity, would seem a logical course to adopt. An encouragement to continue work in other cases, making the maximum use of residual capacity (even though the skin may not be spotless), would, as a corollary, seem a useful measure towards rehabilitation.—I am, etc.,

Middlesbrough. JOHN K. MORGAN.

SIR,—As an industrial medical officer, I hope I may be allowed to comment on some points mentioned by Dr. F. F. Hellier and by Dr. H. R. Vickers in their very practical papers (*Journal*, January 25, pp. 196 and 199).

In the aero-engine factories of which I am medical officer there has been established for the past 10 years a system of working, based on the principle of minimal contact with skin irritants, which has resulted in the incidence of occupational dermatitis having been reduced to negligible proportions in a working population of around 7,500. The cases which do occur are seen in their earliest stages, are advised and encouraged to stay at their jobs with personal medical supervision, and, if necessary, are reinstructed to use the protective measures provided for them. The number of employees who went off work and who received industrial injuries benefit from the Ministry of National Insurance during the past 10 years has averaged four per annum; and the average period off work was 4.5 weeks. I have found that the financial status of the family group to which an employee belongs is an important factor in making him or her decide whether to continue at work or not. Thus, a middle-aged employee with a grown-up family, whose wage-packet is one of several coming into the household, will more readily go off work than a younger colleague with the same type and degree of industrial dermatitis who is the sole wage-earner in his family.

I was interested in Dr. Vickers's paper particularly where he states that, among 250 steelworkers, there was an incidence of 87 cases (34.8%) of dermatitis caused by the use of acriflavine and its analogues, and penicillin, in the treatment of minor injuries at work. Perhaps my experience on this subject from within the industrial environment may have some relevancy. During the past 10 years the total number of minor injuries, such as cuts, lacerations, abrasions, and

punctured wounds, which were treated, after preliminary washing with soap and water, with 1% cetrimide and proflavine dressings, was 138,600, a yearly average of 13,860. There has not been a single case of sensitization dermatitis with this regime, though I am aware that a small proportion of workers are hypersensitive to the application of acriflavine. Similarly, burns and scalds, with an annual incidence of 860 over the past 10 years, and the 2,480 wounds which I have sutured in the same period, have been treated with penicillin ointment, 1,000 units per gramme. Again, there have been no cases of sensitization dermatitis. If these results are similar to those in other industrial medical departments, it follows that, relative to the total number of minor injuries treated with acriflavine—or, better still, proflavine—and with penicillin over a given period, the incidence of sensitization dermatitis caused by such agents must be very small indeed.—I am, etc.,

Glasgow. EDWARD COLLIER.

Common Cold: Fact or Fancy?

SIR,—The report of the discussion by the Section of General Practice at the Royal Society of Medicine, entitled "The Common Cold: Fact and Fancy" (*Journal*, January 25, p. 214), records more fancies than facts. Dr. R. E. Hope-Simpson's figures that for the past five years 350 volunteers had an average of seven colds each year, with an annual morbidity of 70 days, are clearly grotesque. The average incidence of colds over the country as a whole, as taught me by Professor C. H. Browning and in keeping with my experience, is not more than two per annum. Any individual who suffers from appreciably more than this figure is the victim of vasomotor rhinitis—with its many and varied stress causes. As instances of the latter, let me quote the following examples in different age groups:

Girl of 24 years, about to be married to a young man with a strong history of alcoholism, develops a streaming, afebrile cold, not influenced by antibiotics, but cured in a matter of minutes by antihistamines.

Man of 48 develops an afebrile cold three days before he is to be operated upon for suspected carcinoma of bronchus. This cleared up miraculously on antihistamines.

Elderly gentleman, retired and apprehensive, required to act as chairman to important gathering, develops a cold 48 hours before the occasion. This also clears up at once with antihistamines.

The above are not unusual cases, and in my experience anybody who constantly has more than two colds in a year can be benefited greatly by the intelligent use of antihistamines. These must be given in the earliest stages, and once secondary catarrhal infection has developed they are better discontinued and replaced by preparations containing ephedrine. It is realized that the "cold" which spreads from one member of a household to another is likely to be a true infection, and therefore not likely to be averted by antihistamines, but surely this does not happen seven times a year and afflict one one day in five!—I am, etc.,

London, W.1. RALPH SOUTHWARD.

Anticonvulsants and Megaloblastic Anaemia

SIR,—The recent article by Drs. P. Kidd and D. L. Mollin (*Journal*, October 26, 1957, p. 974) prompts us to record another case of megaloblastic anaemia associated with anticonvulsant therapy. In the 27 cases which have been reported, the state of nutrition, laboratory findings, and appropriate therapy have varied considerably. These drugs cannot yet be firmly incriminated, as is shown by Gydell's review.[1]

A 24-year-old female epileptic presented with a haemoglobin of 8.5 g. per 100 ml., R.B.C. 1.9 million per c.mm., and M.C.V. 138 c.microns. No oral or haemorrhagic manifestations were present. Serum vitamin B_{12} was 160 $\mu\mu$g. per ml.; free acid present on gastric analysis; fat balance and liver function tests normal. Anticonvulsant therapy had consisted of phenobarbitone, gr. 1 (65 mg.) twice daily for six years, with the addition of primidone, 750 mg. daily for two and a half years before admission. For the last six months her diet had been conspicuously lacking in animal protein and fresh vegetables.

Before marrow puncture was performed, ascorbic acid was given orally without alteration in the blood picture. The marrow showed a reversed myeloid:erythroid ratio with a marked shift to the left in erythropoiesis. The early forms were megaloblastic, but only an occasional later form showed minor abnormalities in chromatin pattern resembling the picture described by Varadi.[2] Howell-Jolly bodies and giant metamyelocytes were present, indicating that the disturbance did affect later forms of maturation. There was a striking dissociation between marrow and blood pictures, but, as review of the literature shows, marrow findings are not uniformly like this. This was exemplified by another case attributable to phenobarbitone only, with a haemoglobin of 4.6 g. per 100 ml., in which the marrow resembled that of pernicious anaemia. Dr. Varadi does not state the level of haemoglobin in his cases and the degree of anaemia will obviously affect the marrow picture. Concomitant vitamin C and/or protein deficiency may also be required to produce the "full-blown" megaloblastic marrow. Oral folic acid in this case produced a satisfactory rise in haemoglobin and R.B.C.s whilst anticonvulsant therapy was continued.

In support of a direct relationship between anticonvulsants and the anaemia is the fact that where primidone has been incriminated the average duration of therapy has been one and a half years, whereas with phenytoin sodium this has been five years. This difference may be attributed either to the closer structural similarity of the former drug to folic acid or to the higher dosage employed. This comparison, however, does not take into consideration the amount of phenobarbitone, which most patients have also received.—We are, etc.,

D. W. DAWSON.
Manchester, 8. J. JOHNSON.

REFERENCES

1 Gydell, K., *Acta haemat.*, 1957, **17**, 1.
2 Varadi, S., *Lancet*, 1957, **2**, 846.

Problems of Puberty

SIR,—There appears to be a tendency amongst medical men who refer to masturbation to condone it, and recently some have gone even further. Dr. Douglas Hubble (*Journal*, January 25, p. 191), in referring to Kinsey's figures, describes the minority who do not masturbate as the "abnormals." It seems a little hard to be labelled as abnormal because one exercises rather more self-control than one's fellows. Is the scholar "abnormal" because he excels in knowledge or application?

The figures (Kinsey's) which Dr. Hubble quotes for America are staggering and, of course, cannot be very reliable. But two years' experience as a resident medical officer at a British public school convinces me that the incidence here is much lower. I cannot believe that a boy who masturbates daily is doing himself no physical harm. I could instance many cases where a boy's deterioration or advance both mental and physical can be traced from the time of this adoption or abandonment of this evil practice.

Furthermore, no doctor worthy of the name can divorce himself from the moral implications. A boy usually commences masturbation from a combination of curiosity and urge, and this is the time when wise advice can help him most. It is a short step from this stage to that of deliberate auto-eroticism aided by the mass of pornography which our modern "Welfare" State places in the hands of youth. The result can be deplorable and is probably at the root of a great deal of juvenile delinquency. It is time the medical profession ceased this attitude of *laisser faire* and at least discouraged this revolting practice.—I am, etc.,

London, N.W.1. R. N. B. BYATT.

SIR,—Quoting Kinsey *et al.* as saying that 90% of American males have masturbated by the time they are 17 years of age, Dr. Douglas Hubble (*Journal*, January 25, p. 191) goes on to declare that "the abnormal boys, then, are those who do not masturbate." Presumably the words used say a little more than he meant to say, otherwise the deduction is not fully logical. In any case, Kinsey's statistics relate to a world in which true religious influences are sadly admitted to be at a comparatively low ebb. Dr. Hubble exhorts doctors to base their advice to adolescents on these

premises. The easygoing outlook which results is very much in line with so-called modern trends of thought, and is likely to become even more generally accepted than it already is. One feels, therefore, that there is considerable danger that some of the few may have their resolution weakened by the apparent weight of evidence against them, and abandon even the attempt to follow the stony, though richly rewarding, path of self-control. May a word then be put in for the encouragement of these? The Bible abounds in examples of minorities who, although no doubt often thought "abnormal" by the majorities, were by no means therefore wrong.—I am, etc.,

Litcham, King's Lynn. E. A. KNAPPETT.

Abnormal Responses to Muscle Relaxants

SIR,—Dr. P. B. Croft's paper (*Journal*, January 25, p. 181) was of interest because of his collection of cases showing neuromyopathy in association with carcinoma affecting especially the bronchus. I am, however, far from convinced from the evidence supplied that any of these showed real sensitivity to the relaxant drugs.

There are many factors that could have led to the sequence of events described in Case 1, in particular the two incidents of hypoxia, one in the theatre and one on the way back to the ward. No neostigmine appears to have been given until the emergency had arisen, and by that time a degree not only of hypoxia but also of hypercarbia would be present. Here, as in the other cases, no doses are given either of the relaxant or of the antidote. The data given in regard to Case 2 are also quite inadequate to justify the diagnosis. There are no details of pre-operative lung function, and many causes of the picture of respiratory depression in such patients other than sensitivity to relaxants must be thought of—in fact, it is best to arrive at this conclusion only when all other possible aetiology has been definitely ruled out. It would also appear that here, as in Case 5, neostigmine was given before spontaneous respiration was present, a practice which is only likely to lead to confusion in diagnosis. In Case 4 there is little reason to attribute post-operative weakness in a man of 68 to gallamine, especially when he had been complaining of this for some time before his operation. Had Sir Russell Brain seen him pre-operatively he might have found little change at his post-operative examination.

It is postulated by Dr. Croft that these patients may show sensitivity to both depolarizing and non-depolarizing agents, and that in Case 3 weakness, again present and complained of before operation, was exacerbated for two weeks by suxamethonium. Perhaps the muscle pains associated with the administration of this drug played a part here. I do not deny that in cases showing evidence of neuromyopathy changes in sensitivity to these drugs may occur, but I do not think that Dr. Croft has produced any real evidence. Many hundreds of patients with bronchial carcinoma have been anaesthetized for bronchoscopy and operation without evidence of such sensitivity. Finally, once again may one plead for the use of test doses of non-depolarizing agents. They might well be found useful in such cases.—I am, etc.,

Liverpool, 7. T. CECIL GRAY.

SIR,—Anaesthetists would welcome the paper by Dr. P. B. Croft (*Journal*, January 25, p. 181) more if full accounts of the anaesthetic techniques were included. Relaxant drugs are blamed for mortality or morbidity in five patients, but even the doses are not mentioned.

In Case 1 the coma was surely more likely to be caused by the episodes of asphyxia than by any abnormal or central action of gallamine. With Case 4 the relation between the use of gallamine and the inability to stand up four days later is rather remote for direct cause and effect. In Cases 2 and 5 a test dose of D-tubocurarine would have given the warning and avoided the overdose, and many anaesthetists regard this as normal practice in the use of the drug. In Case 3 it is important to know the reaction to the suxamethonium. Was the response noted to be abnormal by the anaesthetists at the time, and, in particular, did the patient's muscles fasciculate? This man was suffering from a neostigmine-resistant neuromuscular disorder of over six months' duration. Suxamethonium fasciculation may involve much more muscular activity per unit time than is usual for the individual, as is shown by the muscular pain and stiffness which frequently follow its unmodified administration. If fasciculation occurred in this weak elderly man, it does not surprise us that he took a fortnight to recover his previous state. Alternatively the reaction could have been myasthenic in type, with feeble fasciculation, incomplete paralysis and the slower recovery characteristic of an anti-depolarizing type of neuromuscular blockade. We think that this patient's muscles must have fasciculated as expected because neostigmine did not help his weakness, but without more information further argument becomes mere idle speculation.

We do not underestimate the value of this paper. Dr. Croft has done us a service by pointing out a possible hazard in the investigation on surgical treatment of cancer. Nevertheless, it would be a pity if patients with a suspected bronchial carcinoma were to be refused general anaesthesia for bronchoscopy because of his conclusions and recommendations.—We are, etc.,

DAVID BROWN.
London, E.2. J. V. I. YOUNG.

Techniques of Psychotherapy

SIR,—Dr. E. A. Bennet, who reviewed my book *A Short History of Psychotherapy in Theory and Practice* in your issue of January 11 (p. 89), has recognized it more clearly than most reviewers as an attempt to penetrate behind the smoke-screen of psychotherapists' own theoretical explanations and compare these with what they actually do to their patients. I am replying to his criticisms only because he seems to me to see the point of my approach without being able to face its logical consequences.

This explains, for example, why he thinks I have given too little space to Jung (although Jung is in fact the subject of two out of the eight historical chapters). Jung's theoretical writings may equal, or even exceed, Freud's in volume, but his technical innovations, important as they are, do not take so long to describe. Dr. Bennet also criticizes the well-supported view that Jung's uneasiness about the Freudian emphasis on sex was the main reason for his apostasy. I know that other and more theoretical reasons were put forward, and my book deals with them briefly; but the practical issue seems to have been whether it was essential to talk to patients about sex, and the theoretical arguments which followed were probably attempts to confuse the main issue.

Dr. Bennet is surprised by the suggestion that all modern psychotherapeutic methods are descended from those of Mesmer. I am not sure whether he is denying my facts or my interpretation of them. Briefly: Freud's own autobiography acknowledged his debt to the hypnotic technique of Bernheim, who derived it, through Liébeault, Braid, and Lafontaine, from Mesmer's French imitators. Adler's and Jung's subtechniques were modifications of Freud's, which both at first imitated. Coué's technique of non-hypnotic suggestion was derived from the Nancy school founded by Liébeault and Bernheim. It goes without saying that all these psychotherapists owed something to other influences, but I cannot see how anyone could, or should want to, deny their common ancestor.

I do, however, agree with Dr. Bennet that I should have distinguished clearly between Freud's method of "free association" and Jung's amplification.

I am glad that he approves my suggestion that the efficacy of treatment depends even more than most modern psychotherapists think upon the handling of the transference. He calls this, however, "the incommunicable element in treatment," and says that few practising psychotherapists will agree that it could become a communicable part of technique. Admittedly the best practitioners of a method are not always able to say how they do it: but surely all the papers on this subject by Freudians, Jungians, and others are not quite devoid of meaning. Even if they were, trainees learn a lot by imitation. Certainly no improvement in technique is likely to result from the rather mystical assumption (against some evidence) that the most important bit is "incommunicable."

I hope that Dr. Bennet will recognize this reply for what it is—a tribute to the importance of his criticisms. If I ever achieve a second edition I shall try to meet some of his points.—I am, etc.,

Edinburgh, 9. NIGEL WALKER.

Bedside Test for Proteinuria

SIR,—There has recently been marketed in the United States of America a new product known as "albustix" for the detection of protein in the urine, and I understand it is shortly to be available here. The test is extremely simple to perform, being very similar to the new enzyme test-sticks (e.g., "tes-tape" and "clinistix") for the detection of glucose. A stick of thick paper is impregnated at one end with the reagents. Dipped into urine the impregnated end turns green if protein is present in the specimen.

The reaction is based on the protein error of indicators.[1] The impregnated end of the stick is buffered to a *p*H of approximately 3. The buffer prevents the influence of the urine *p*H on the test, so that the indicator is affected only by protein if present. The test is not affected by the turbidity of the urine—*filtering is unnecessary*. Nor is it necessary to transfer the specimen into a test-tube. These two advantages, possessed by no other test for proteinuria, make albustix a very useful addition to the general practitioner's diagnostic kit.

I have recently been testing the sticks under practice conditions and have now performed over 200 tests. In each case the sticks were compared with 25% salicyl-sulphonic acid (5 drops to 4 ml. of urine)—I have long ago given up boiling urine in my practice without any loss of accuracy, and with considerable improvement in my temper. *I found no false negatives*. However, on many occasions a faint green colour change was recorded. This occurred twice when the salicyl-sulphonic acid detected a cloud, but at all other times the latter test showed an absence of protein. It was only in the last 50 or so tests that I noticed that this false weak-positive was found mainly in the urine of women of child-bearing age, and since then I have found it in only one male. Among pregnant women (in my antenatal clinic) this reaction seemed to occur in more than half, but I would stress that I have not tested it sufficiently since I noted the coincidence.

On the other hand albustix are capable of detecting protein in very weak dilutions. I added as little as two drops of the urine of a nephrotic patient to protein-free samples of urine, and, on each of the four times I tested it, was able to get an easily recognizable positive reaction. The American samples of the sticks I tested had with them a quantitative shade chart, which I found of little help, except that all the false weak-positives were of a shade between negative and the lowest positive (30 mg.%). In the case of positive results, it was not uncommon to get a range of shades.

In my opinion the sticks will be very useful to G.P.s, particularly at the bedside, when all that is necessary for the detection of protein is to dip the stick into the chamber-pot of urine. Once one is familiar with the limitations of the false weak-positive reactions I have described, they present no problem. If any doubt exists the urine could always be tested with salicyl-sulphonic acid. The price has still to be fixed, but I am told it will be about a penny a stick.—I am, etc.,

London, W.12. STUART CARNE.

REFERENCE

1 Feigl, F., *Spot Tests in Organic Analysis*, 1956, pp. 401, 402. Cleaver-Hume Press, London.

Artificial Insemination

SIR,—May I express my agreement with the views put forward in the letter published in your issue of January 25 (p. 222) over the signature of Dr. Dorothy E. Peake, who describes the practice of A.I.D. as a revolting conception, contrary to human dignity and the integrity of the family?

Some 14 years or more ago, when A.I.D. was first being actively mooted, I wrote a letter[1] which was published in your columns wherein I made a plea that the medical profession should beware whither they were bound in condoning such a practice, for, once ethical standards are relaxed, "*facilis descensus Averno*." I was then a lone voice, but about a year later the late Sir Leonard Parsons,[2] the well-known Birmingham paediatrician, with some others wrote in your columns to condemn this practice.

It is, in my view, deplorable that any member of the profession should consider the practice of A.I.D. one in which he or she can take part with a clear conscience. And what, one may ask, must one think of the mentality of the so-called donor?

I am uncertain whether the Ethical Committee of the British Medical Association has expressed an opinion about this practice, but a few years ago some evidence was given before the Royal Commission on Marriage and Divorce on behalf of the B.M.A. which seemed to condone the practice of A.I.D.,[3] and I believe that this evidence was subsequently withdrawn[4] because it was repudiated by the general public opinion of the profession. It is surely overdue that an authoritative opinion should be published on the ethics of this practice.—I am, etc.,

Lodsworth, Sussex. J. R. A. TODHUNTER.

REFERENCES

1 *Brit. med. J.*, 1944, **1**, 25.
2 Ibid., 1945, **1**, 96.
3 Ibid., *Suppl.*, 1952, **1**, 188.
4 Ibid., *Suppl.*, 1952, **2**, 41.

SIR,—The patients who come to us for A.I.D. are surely sadly disillusioned people. They have not come merely for the cure of their childless state—adoption would be a much surer and altogether easier method of solving that problem. The act of falling in love having failed to satisfy them, they hold the view of many an otherwise enlightened spinster that pregnancy is not only productive of a most desirable infant but a potent magic called "mother love," calculated to turn an ordinary female into a perfect angel with enough patience to outlast the demands of the most difficult childhood and the vagaries of adolescence.

In my experience pregnancy is far more likely to be productive of nausea, and even vomiting, than of any magic. The disturbed nights following on a day's hard labour should suffice to convince any mother that true "mother love" is a hard matter of discipline and unselfishness. Love is God's own production and cannot be obtained by contravening His laws. If we cannot tell our patients how to come by it, then let us at least refrain from adding to their disillusionment and sorrow.—I am, etc.,

Bristol, 8. GRACE HARLAND.

Treatment of Leg Ulcers

SIR,—I have read with interest the recent correspondence about leg ulcers and entirely agree that most cases can be cured by firm pressure over a pad. But what is the right treatment for the elderly patient with arteriosclerosis and signs of severe arterial insufficiency in the lower limb? I have had several of these to deal with lately, and although I should like to bandage firmly I am afraid to do so.—I am, etc.,

Hove, 3. VERA E. CLAXTON.

SIR,—I must agree wholeheartedly with Mr. A. Dickson Wright (*Journal*, January 25, p. 221) in his condemnation of spread of leg ulcer treatment into the hands of ancillaries. The complaint that these patients voice most often in their sad pilgrimage from hospital to hospital is the lack of continuity in treatment—"We never see the same person twice." The tendency to encourage physiotherapists and nurses to carry out the actual details of treatment can only be a retrograde step, and is the negation of everything that Mr. Dickson Wright has stood for since he first waved the green flag of elastic adhesive ambulatory compression in 1927, giving the all-clear to gravitational leg ulceration. But yet with present-day meagre facilities I cannot see how any other course is possible. There are some 250,000 leg ulcers in Great Britain, including 25,000 in the London area alone. The demand for treatment is far greater than the present facilities permit and inevitably leads to hurried, overcrowded sessions with "farming out" of the unfortunate patients to co-workers, who may have neither the time, the interest, nor the experience to greatly benefit those under their care.

As I write I have before me a Report of the Committee on Fractures, appointed by the British Medical Association in

1933, "to consider the existing arrangements for the treatment of fractures and other associated injuries of the limbs and to make recommendations for possible improvement thereof." The Committee was set up as a result of growing dissatisfaction with the facilities available at that time for the satisfactory treatment of acute bony injuries. Surely there is the same crying need to-day for such a study to be made of the "existing arrangements" for the treatment of ulcerated legs and varicose veins.—I am, etc.,

London, N.W.1. STANLEY RIVLIN.

Influenza

SIR,—In view of the present interest in Asian influenza the following notes may be of interest. In Europe in late 1945 there was an outbreak of influenza. My hospital admitted its first three cases on November 24, 1945, and within seven days 78 cases in all had been admitted. Observations on 355 consecutive cases treated between November 24, 1945, and January 14, 1946, are as follows:

All cases presented the following clinical manifestations: Sudden abrupt onset of a short-term febrile illness with shivering, headaches (frontal, retro-orbital, and eye-ache), dizziness, muscle and joint pains, apathy, marked weakness and anorexia, sore throat, and a harsh, dry, frequent, irritable, barking, and unproductive cough. Also signs of tracheitis with minimal bronchitis. All cases were feeble and weak when they first got out of bed (48 hours after the end of pyrexia in uncomplicated cases) and took several days to find their feet. In addition the irritable cough persisted in some cases for several days. The white blood cell counts, total and differential, were within normal limits in the uncomplicated cases and showed no distinctive features. The systolic blood pressure in some of the uncomplicated cases fell as low as 100 mm. Hg, and these cases complained particularly of feeling "played out." There were many such cases among the older subjects. They just wanted something to relieve their headaches, aches, and pains, and to be left to lie and sleep undisturbed.

Of the 355 cases studied, 225 (63.4%) were uncomplicated. Their average duration of pyrexia, delay before admission, and period in hospital were 3.34, 3, and 9.6 days respectively. The duration of the stay in hospital was largely determined by the need for beds.

The remaining 130 cases (36.6%) shared additional features or complications to their influenza as follows: *laryngitis* (32 cases); *sinusitis* (29 cases); *lymph node enlargement* (29 cases): essentially of the tonsillar and posterior cervical nodes and sometimes the axillary and/or inguinal nodes also but never the epitrochlear nodes; in 5 cases the spleen was palpable; *diarrhoea and vomiting* (15 cases); *otitis media* (5 cases, 2 of which required myringotomy); *dry pleurisy* (5 cases); *epistaxis* (4 cases); *cyanosis* (2 cases); *pleurisy with effusion* (1 case); *lobar pneumonia* (radiological diagnosis, 6 cases; with dry pleurisy, 3 cases; with clear pleural effusion, 1 case; with empyema, 2 cases); *bronchopneumonia* (7 cases, of which 2 had dry pleurisy); *pneumonitis* (16 cases).

All cases of lobar pneumonia, bronchopneumonia, and pneumonitis—complicated or uncomplicated—were treated with sulphathiazole by mouth or penicillin intramuscularly or both together. In none of the pneumonic cases without pleurisy, etc., was there a sudden drop of temperature under the drug therapy adopted. Nor was there any definite correlation between the response to drug treatment and the degree of polymorphonuclear leucocytosis in the peripheral blood or the sensitivity of the predominant organism in the sputum. The inference was that, although the secondary invader was being controlled, the initial invader—namely, the virus of influenza—was relatively unaffected.

Only 15 out of 355 cases showed gastro-intestinal symptoms. In this epidemic the respiratory system was predominantly affected. There were no fatal cases. Unlike the R.A.F. cases[1] and the Army Chest Centre series of viral respiratory infections[2] every case did not have a radiograph of the chest. I feel that a better descriptive term for the pulmonary opacities than segmental aspiration pneumonia would be segmental (or zonal) atelectasis due to adhesive bronchial pneumonia.[2]—I am, etc.,

Kinrara, Malaya. J. MACKAY-DICK.

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1 Gilroy, J., *Brit. med. J.*, 1957, **2**, 997.
2 Mackay-Dick, J., Elliott, J. G., and Jones, C. H., *J. roy. Army med. Cps.*, 1955, **101**, 292.

Patellar Dislocation and Chondromalacia

SIR,—The paper by Mr. H. H. Langston (*Journal*, January 18, p. 155) I find both interesting and instructive. I should welcome his comments on the following points. He states that subluxation of the patella is a more common injury than is often thought, that if recurrent it is a common cause of chondromalacia patellae, and he recommends what appears to be rather drastic revolutionary treatment. Has he tried the effect of a long period of rest from strain?

Chondromalacia patellae has a number of causative features and clinical signs which are common to the better-known condition of osteochondritis dissecans, most commonly found in the articular surface of the medial femoral condyle, but which I have recorded[1] in the articular surfaces of the patella, the lateral femoral condyle, the femoral capital epiphysis, the capitellum, the head of the radius and humerus, the navicular, the astragalus, the head of the first metatarsal, and the lower end of the tibia; in these cases the diagnosis was aided by radiography, either because the damaged articular surface carried with it a flake from the surface of the bone, or because time had permitted the deposition of calcium in the detached fragment. Most surgeons would admit of the difficulty of diagnosing osteomalacia patellae from or in addition to ligament or disk damage, since radiography is usually of no value, unless it is associated with bone damage or deposition of calcium, as indicated from the results of operations on the menisci, etc. Even with the most careful scrutiny during operation the complete extent of the damages suffered may not be recognized, and, as Mr. Langston shows, patellectomy may not free the patient from all signs and symptoms. Is it not unusual to remove the damaged articular surfaces of other bones?

Since we know that considerable restitution of articular surfaces can take place during rest, may it not be likely that longer rest, exacting and difficult though it may be, would give ultimately a greater reward? I showed[2] that if the joint in Perthes's disease was freed from strain, even for as long a period as four years, while the condition was active, a normal joint, in which no secondary changes developed, resulted. We have seen this in cases of damage to other articular surfaces. In a letter I have, dated February 11, 1932, from that leader in orthopaedics, Sir Robert Jones, he stated that he was impressed with the importance of the gentle hand: "Surgeons too often meet with distressing results due to rough and ruthless manipulation." Far be it from me to suggest that any surgery could be so described, but it would appear to be more permanently damaging than the recognized trauma which caused the lesion.

I have referred[1] to the case of a boy of 16 years with recurrent dislocation of the patella who had not only damage to the articular surface of the patella but also the separation of a fragment from the articular surface of the lateral femoral condyle one inch (2.5 cm.) long; can we be sure that no such damage has occurred, since the damaged fragment may not be shown as in this case? Might rest not give both surfaces a chance of restitution?—I am, etc.,

Birmingham, 15. JAMES F. BRAILSFORD.

REFERENCES

1 Brailsford, J. F., *The Radiology of Bones and Joints*, 5th ed., 1953.
2 —— *Brit. J. Radiol.*, 1935, **8**, 87.

Familial Incidence of Addison's Disease

SIR,—Under my care at the moment is a boy who is the second in his family to develop Addison's disease in the second decade of life. The memorandum of Dr. P. H. Hewitt (*Journal*, December 28, 1957, p. 1530) and the letter from Sir Charles Symonds (*Journal*, January 11, p. 100) are therefore of particular interest. For those who may be interested, a few details of this patient are given below.

Aged 14 years, he presented in March, 1957, with a history of nocturnal enuresis dating from infancy. He had suffered from severe alopecia for six years, for which he had been provided with

a wig. On physical examination nothing abnormal was noticed. The history, however, was obtained of Addison's disease in a sibling who died in 1953, at the age of 18 years. The diagnosis in this girl was fully established by my colleague, Dr. E. G. Rhind. She died suddenly at home whilst under treatment. A necropsy was not performed. There is one other child in the family, now aged 20 years, who is well.

During the present patient's attendance for enuresis, it was noted that his skin was becoming pigmented and he was admitted for further investigation. By this time he was an ill, lethargic-looking child with some clinical dehydration and a blood pressure of 120/60: his skin was diffusely pigmented and there were also brown, localized patches on the face and limbs: these were also present in the mouth. His Mantoux (1/1,000) was negative. Laboratory investigations fully confirmed the diagnosis and the Kepler ratio was as low as 1.86. Since his serum sodium was only 120 mEq./l. treatment was started shortly after admission.

He has responded well and is now a cheerful, alert boy without any pigmentation. He is being treated with cortisone and 9-alpha-fluorohydrocortisone. Whilst on this he developed latent tetany which was thought to be secondary to hypokalaemia due to an excess of the latter drug. He was at that time having 0.2 mg. 9-alpha-fluorohydrocortisone and 12.5 mg. cortisone twice daily. The dose of 9-alpha-fluorohydrocortisone was therefore reduced to 0.1 mg. twice daily. The latent tetany has since disappeared and his serum potassium has risen from 3.7 mEq./l. to 4.6 mEq./l. So far, however, he still has his alopecia—and his enuresis.

—I am, etc.,

Sheffield. R. R. GORDON.

Unusual Case of Strangulation

SIR,—I have under my care a child, aged 2 years, who had a vaccinia encephalitis a year ago and recovered. She was playing merrily in the playpen last week. Mother, who was working in the adjacent kitchen, did not hear any sound for a few minutes and went through to find her strangulated. Apparently what had happened was that the sleeve of the child's jumper had caught in the small catch on the folding side of the playpen. The child had pulled her arm out of the sleeve and fallen, slipping on the rug on the floor of the playpen. On release she was unconscious for approximately five minutes, and came round quickly without artificial respiration.

On examination an hour and a half later, the child had typical petechiae from the neck upwards, a thin blue line where the edge of the jumper had caught her round the neck, and several blotchy patches on her cheeks. She refused her lunch that day, but apart from that appears to have suffered no ill effects. On examination of the playpen, it appeared that the retaining peg upon which she caught her jumper only stuck out about one-eighth of an inch (3 mm.). It seems remarkable that such a small object could have had such potentially severe consequences.—I am, etc.,

St. Albans, Herts. J. DOUGLAS JOHNSTON.

Resuscitation

SIR,—Dr. O. P. Llewellyn has warned your readers (*Journal*, January 4, p. 42) that a machine like the "Stephenson Minuteman Resuscitator" cannot be effective without the introduction of an endotracheal tube. I have used this resuscitator in curarized subjects without an endotracheal tube and am convinced that it is possible to make it effective, provided the operator is capable of maintaining a free airway. When I connected the resuscitator to an endotracheal tube in a patient the machine could not be made to function. The reason why the machine will not function via an endotracheal tube is that the internal diameter of the tube is small enough to cause a viscous resistance so that the triggering pressure is rapidly reached and the machine "chatters."

I agree that oxygen, when given by means of the Stephenson Minuteman Resuscitator via a mask, may find its way into the stomach, but it also gains access to the lungs provided the airway is clear. I have a record in which the expired gases were obtained by a small catheter inserted into a face mask during intermittent positive pressure artificial respiration with the resuscitator in a curarized subject. The carbon dioxide concentration curve, as shown by the rapid infra-red method, appeared with the normal range.

Although a specialist anaesthetist can maintain adequate pulmonary ventilation with the resuscitator without intubation, great care will have to be taken to ensure that first-aid personnel receive a thorough training if they are to apply this method. The machine does supply oxygen under pressure and it might save life in an emergency, even if some respiratory obstruction was caused by the administrator. The danger is that a person who is inexperienced in the art of maintaining a free airway is likely to apply the mask loosely so that leakage prevents inflation of the lungs; alternatively, the mask will be applied with sufficient force to prevent leakage but the jaw is likely to be pushed backwards to obstruct the airway. Explanations of how to support the jaw and at the same time secure the mask in good apposition are not sufficient. Practical experience can only be gained in the anaesthetic rooms of general hospitals where anaesthetists daily use the intermittent positive pressure method of artificial respiration. Practice with mechanical models alone would be ineffective.

No one, faced with a respiratory calamity, should waste time trying to apply a method with which he is unfamiliar. The intermittent positive pressure method is not for those whose training has been limited to methods which involve alterations to the thoracic cage by manual manœuvres.—I am, etc.,

Leeds, 2. R. P. HARBORD.

Maternal Anaesthetic Deaths

SIR,—Dr. D. D. Davies (*Journal*, January 25, p. 217) gives nine rules of safety for conducting anaesthesia in the lithotomy position for forceps delivery. I think he has missed two obvious and valuable safeguards. (1) A cuffed endotracheal tube in its proper place reduces the danger of aspiration of vomitus to nil; (2) an obstetric table which can be tilted quickly, easily, and with one hand is more satisfactory than a nurse standing by to turn the patient to semi-prone at the approach of danger. Women at term are inclined to be heavy, and not all midwives are Amazons.

It may be argued with truth that the period of greatest danger of vomiting is between the beginning of induction and the insertion of the endotracheal tube if this is used, so that intubation is of limited value. This period, however, can be kept short by the use of a moderate dose of thiopentone and a short-acting relaxant. I would heartily agree with Dr. Davies's ever-ready sucker at this stage. I have not found that thiopentone and suxamethonium used in this way appear to affect the babies adversely. (Dr. Davies's remark about 100 dead foetuses is too appalling for comment.) With the cuffed tube in place the anaesthetist is in a position from which he can more readily direct resuscitation of the baby or the mother should either become necessary.—I am, etc.,

Co. Londonderry, N. Ireland. C. A. G. ARMSTRONG.

SIR,—I have read with great interest the correspondence by Dr. A. H. Morley (*Journal*, November 9, 1957, p. 1115) and Dr. D. D. Davies (*Journal*, January 25, p. 217) on maternal anaesthetic deaths due to inhalation of vomitus, as I witnessed such a disaster shortly before entering general practice.

May I suggest that the safest form of anaesthesia for delivery is pudendal block? Now that a really potent anaesthetic agent, lignocaine hydrochloride, is available, and hyaluronidase to spread it, the technique presents no great difficulty. Pudendal block allows the single-handed practitioner to deal, unhurriedly, with low- and mid-cavity forceps, breech deliveries, and also rotations using Kjelland's forceps. With the exception of manual removal of the placenta and manual rotation of a malposition, any procedure which cannot be done under pudendal block should probably not be done in the home.—I am, etc.,

Drayton, Norfolk. JOHN N. GALE.

First Tuberculosis Dispensary

SIR,—Drs. W. Hartston and W. F. Wheeler stake a claim for a house, 6, Liverpool Street, in the City of London, which they call the Liverpool Street Dispensary (*Journal*, February 8, p. 339). If Sir Robert Philip were to read their letter, I hazard he would say, "My children, it matters little that buildings called dispensaries to deal with 'the indigent portion of the population' existed long before my three rooms at 13, Bank Street, Edinburgh, but it matters a great deal what kind of work was attempted in the older dispensaries or out-patient departments of chest hospitals compared with the plan, outlook, and kind of work in my Edinburgh dispensary and others like it."

I am old enough to have had experience of both in my native city of Liverpool, and the difference was great. 13, Bank Street, Edinburgh, was opened to provide a place where an original idea might be worked out for the *prevention* and treatment of an infective disease, tuberculosis. The two main elements of this idea were that patients suffering from tuberculosis must be *sought out* by the physician and that, when found, not just the patient but *the whole family* must be the unit for investigation, medical and social. Now the old Edinburgh (and other town) dispensaries had for years handed out drugs, advice, and a little social help to all and sundry who came—an alleviation chiefly of symptoms. But here in Bank Street was a new, a preventive outlook. To establish tuberculosis dispensaries and the new teaching required years of strenuous work against opposition composed of ignorance, inertia, and not seldom the vested interests of the established chest hospitals with their honorary staffs. As Professor John Crofton has written,[1] "When Koch discovered the tubercle bacillus, Robert Philip appreciated at once that tuberculosis could theoretically be prevented. His great contributions were his faith that this theoretical possibility could be realized and his conception of an organization designed to that end."—I am, etc.,

Church Stretton, Shropshire. G. LISSANT COX.

REFERENCE

[1] In *Sir Robert W. Philip, 1857-1939, Memories of his Friends and Pupils*, edited by Harley Williams. N.A.P.T., London.

Psychopathic Personality

SIR,—I read, with much interest, Dr. A. A. Bartholomew's letter on the above subject (*Journal*, January 25, p. 219) In my experience, the frequency of the diagnosis of psychopathic personality varies inversely to the experience of the psychiatrist. It must be remembered that before such a diagnosis can be made one has to eliminate such things as very high-grade mental defect, epilepsy, adolescent instability, intellectual and emotional immaturity, persistent hypomanic states, arrested schizophrenia, concealed paraphrenia, and the sequelae of organic brain conditions—e.g., epidemic encephalitis, juvenile general paralysis, subdural or subarachnoid haemorrhage, temporal lobe contusion, meningitis, etc.

Dr. Bartholomew's views and findings on the role of extroversion in psychopathic states are undoubtedly of interest, and might lead to an interesting piece of research. But I think there are other and more obvious reasons why the extrovert sometimes finds it difficult to conform to social customs rather than that "they acquire conditioned responses by means of classical Pavlovian conditioning with difficulty, and extinguish them with ease." The extrovert has the facility of easy emotional contact with his environment, but such easy emotional contact *per se* renders him much more open to suggestion. (In hypomania, where extroversion is marked, the great danger, even in boys and girls of hitherto blameless character, is moral corruption from the suggestion of vicious associates.) From all this it must not of course be assumed that extroverts are necessarily of poor moral character and introverts of good moral character. There is a great deal more in this than extroversion and introversion, and I think one could say, with reasonable probability, that both St. Paul and St. Peter were extroverts. Psychopathic personality is often diagnosed where the patient commits crime after crime, without much pattern, and with evidently no capacity "to learn from experience." But, even if one can exclude all other possible factors, I do not think we can yet diagnose psychopathic personality. It must be remembered that moral sentiments are not built up by punishment, and unless the patient has had, in his home life or subsequently, ample opportunity and incentive to build up moral sentiments, I do not think we can speak of psychopathic personality. We may certainly speak of psychopathic behaviour, try to find its cause, and apply the appropriate remedy (in some cases we shall be amazed at the response), but I am still unconvinced that anything is to be gained by the "pathology-begging" diagnosis of psychopathic personality.—I am, etc.,

Pinner, Middlesex. ROBERT THOMPSON.

SIR,—Any attempt at establishing objective criteria of psychiatric diagnosis is to be welcomed. However, many such attempts have been invalidated by lack of care in the selection of clinical material subjected to such investigations. It is to be hoped that Dr. A. A. Bartholomew (*Journal*, January 25, p. 219) will avoid this pitfall by first making it clear to himself and others what his diagnostic concept of psychopathic personality is. In speaking of "this group of persons" and of the "unequivocal psychopath," does he mean Henderson's psychopaths, or Schneider's or Kahn's or McCord's, or has he an operational definition of his own? Does he perhaps mean the third of the three main conceptions of the term quoted by Curran and Partridge?[1] The existing confusion about this term is in no small part due to lack of agreement about different clinical concepts. In your recent annotation on psychopaths (*Journal*, December 28, p. 1536) it was noted that the recommendation of the Royal Commission on mental illness to incorporate the term in the new legislation had met with strong opposition from psychiatrists for that very reason. Everybody using the term "psychopathic personality" in practice or research ought to state expressly what he means by it. In failing to do so, Dr. Bartholomew would open himself to the criticism that technical sophistication in the evaluation of data does not exempt the research worker from the requirement of careful selection and description of the clinical material on which he is carrying out his investigations.—I am, etc.,

Sheffield, 10. E. STENGEL.

REFERENCE

[1] Curran, D., and Partridge, M., *Psychological Medicine*, 1955. Edinburgh and London.

Amnion Implantation in Peripheral Vascular Disease

SIR,—The following observations on a case of arterial disease may interest your readers. A doctor colleague of mine in 1955 was suffering from a severe intermittent claudication of both legs, especially the left, and at one time in consultation with other doctors in Australia amputation of the left leg was considered, as a definite popliteal block had been established. Tolazoline hydrochloride and nicotinic acid gave no improvement, and a course of "hydergine" (a mixture of dihydroergocornine, dihydroergocrystine, and dihydroergokryptine) which I instituted produced some improvement. In December, 1956, he could walk only between 30 and 60 yards (27.5–55 m.) before the onset of pain.

Having heard of the work in London of Mr. E. Troensegaard-Hansen, my colleague came over here and had an amniotic implant performed on April 18, 1957. On June 13, 1957, the patient walked with me for about one mile (1.6 km.) on a mild upgrade, stood about in a book shop for 20 minutes, and then took a bus back to his hotel, without feeling any discomfort whatsoever. A recent report by letter from the patient's wife says, "It is really wonderful to be able to go for a walk of a mile or two in the evenings with my husband as we used to five years ago." I trust this factual statement may give encouragement and be beneficial to sufferers from this distressing arterial disease.—I am, etc.,

Sydney, Australia. M. ELLIOT-SMITH.

Heart Disease and Pregnancy

SIR,—Mr. J. B. Das and Mr. J. T. Chesterman in their paper on "Valvotomy in Mitral Stenosis Complicated by Pregnancy" (*Journal*, January 18, p. 142) conclude that valvotomy is an attempt to help the mother who wishes to avoid the frustration of therapeutic abortion and sterilization. This seems to infer a straight choice between surgery and abortion in many cases. Experience of 539 cases of rheumatic heart disease complicated by pregnancy[1 2] has led us to conclude that (*a*) there is no place for therapeutic abortion in the management of this condition, (*b*) valvotomy may be very useful but is rarely indicated during pregnancy.—We are, etc.,

M. I. DRURY.
M. K. O'DRISCOLL.
A. P. BARRY.

Dublin.

REFERENCES

1 Drury, M. I., O'Driscoll, M. K., Hanratty, T. D., and Barry, A. P., *Brit. med. J.*, 1954, 1, 70.
2 O'Driscoll, M. K., Barry, A. P., and Drury, M. I., ibid., 1957, 2, 1099.

Lionel Whitby Memorial Fund

SIR,—We should appreciate your assistance in calling attention to a fund being raised by the Master and Fellows of Downing College, Cambridge, in memory of their late Master, Sir Lionel Whitby, C.V.O., M.C., M.A., M.D., Regius Professor of Physic in the University.

The "Lionel Whitby Memorial Fund" was established at the suggestion of the Downing College Association and an appeal has been sent out to its members. It is proposed to use the fund to found Whitby memorial scholarships in the College, an object which, it is felt, would have met with his warm approval. As an undergraduate of the College he was a Scholar, and later became successively Honorary Fellow, Professorial Fellow, and finally Master, and the College was one of the chief interests of his life. It has been suggested to the Master and Fellows that among his wide circle of friends in the medical world there may be many, in addition to members of the College, who would like to contribute to this memorial fund.

The Master and Fellows would very much welcome such contributions, as the resources of the College are among the most limited of those of the Cambridge Colleges. Although the College now spends from its general resources nearly £4,000 annually on scholarships and exhibitions, only about £1,000 of this is provided from specific endowments. It was the heavy demand thus made on the general endowments of the College, together with a wish to keep alive the memory of Whitby in the minds of future generations of undergraduates, which led the association to allocate the present fund to the foundation of scholarships bearing his name. Contributions should be sent to the Bursar, Downing College, Cambridge, and, if so desired, may be made by seven-year covenant, forms for which will be supplied on request.—We are, etc.,

W. K. C. GUTHRIE. CHARLES DODDS.
GORDON GORDON-TAYLOR. R. W. SCARFF.
HAROLD BOLDERO. JOHN KIRK.

Cambridge.

POINTS FROM LETTERS

Patient's View of Nursing

Mrs. KATHERINE KEMPTHORNE, S.R.N. (London, N.14), writes: The late Sir Ernest Kennaway's article on "Some Notes on Nursing from a Patient's Point of View" (*Journal*, December 21, 1957, p. 1485) is both interesting and amusing and surely a tribute to the nursing profession. Small matters certainly are most important to the patient, and the good nurse takes as much care over the little things as the seemingly more important ones. . . . The strangest hospital rule I have met was while my husband and I were visiting a general hospital in Brussels before the war. We had visited some of the adult wards and came to the children's block, where there was a ward set aside for babies aged 0 to 1 year. Here we noticed a division down the centre of the whole ward, with cots on either side. The sister explained that one side was for "les messieurs," and the other for "les demoiselles." We wondered if they had separate bathrooms, etc., also.

Obituary

GWYNNE WILLIAMS, M.D., M.S., F.R.C.S.

Mr. Gwynne Williams, consulting surgeon to University College Hospital, London, died suddenly at the hospital on February 3. He was 76 years of age.

Gwynne Evan Owen Williams was born at Luton on May 21, 1881, and was educated at Bedford Grammar School. Studying medicine at University College Hospital, he graduated M.B., B.S. from London University in 1903. After holding the appointments of house-surgeon, house-physician, and surgical casualty officer at University College Hospital, he became assistant medical officer at Lewisham Infirmary and then surgical registrar at the Seamen's Hospital, Greenwich. He proceeded to the M.D. in 1905 and the M.S. in 1906, being admitted F.R.C.S. in the latter year. Appointed surgical registrar at University College Hospital in 1910, he was elected assistant surgeon in 1914 and surgeon in 1919. He retired from the active surgical staff of the hospital in 1946. In addition, he was on the staff of the Royal Northern Hospital from 1913 to 1926, and continued to work at the Cheyne Hospital for Children until it was moved out of London in 1939. From 1935 to 1943 he was dean of the medical school at University College Hospital, and was also chairman of the medical committee. A few months before the outbreak of the second world war he was appointed consultant adviser to the Minister of Health on the organization of hospitals in wartime. During the bombing of London he took charge of the casualty services at U.C.H. and lived at the hospital. He also served as a deputy regional blood transfusion officer in the Emergency Medical Service. From 1942 to 1944 he was a member of the B.M.A. Committee on Medical Schools, and an earlier service he performed for the Association was when he acted as vice-president of the Section of Surgery at the Annual Meeting at Oxford in 1936.

Mr. Williams is survived by his widow and three sons, two of whom are in the medical profession. A memorial service will be held in St. Pancras Church, Euston Road, at 12 noon on Monday, February 17.

A colleague writes: Throughout his working life Gwynne Williams practised as a general surgeon, but he early developed and maintained a special interest in the treatment of fractures and, to a lesser extent, in orthopaedics. He wrote little and was not at ease in large gatherings, so that some of his pioneer work remained unknown outside his own hospital. In the early 1920s he was experimenting with the ambulatory treatment of leg fractures by methods later discarded, but novel at the time, and he was restlessly searching for some method of managing fractures of the neck of the femur. He held for some years a somewhat unofficial appointment at one of the hospitals administered by a board of guardians. The superintendent, an old friend, sometimes wanted the services of a surgeon for his patients: these Gwynne Williams provided in return for the right to study and treat fractured femurs, cases which were in those days rapidly removed from the voluntary hospitals as incurable. It was therefore with keen interest that he read of Smith-Petersen's trifin nail operation, and forthwith an order was dispatched to the U.S.A. for the instruments. He was probably one of the first surgeons in this country to insert a Smith-Petersen nail. This interest in surgical technique, perhaps deriving from Arthur Barker, a great technical

surgeon at University College Hospital in the early years of the century, had led Gwynne Williams years before, when surgical registrar, to buy, at his own expense, a cystoscope before there was one in the hospital equipment, and for many years he was the user of a very early and temperamental model of a mechanical saw. Only he and one theatre porter knew how it worked, and its deployment for an operation was fraught with a good deal of stress among the theatre staff. His operating was speedy and confident, without frills, and it was only by seeing how well the patient did that the operating art was appreciated. He was bold at a time when, lacking all the skilled aid given to-day by the anaesthetist, a surgeon needed confidence and courage in tackling difficult problems.

Yet, though his technical achievements were of the highest class, it is probably not as an operating surgeon that old U.C.H. students will recall him, but rather as a teacher and as an example. He expected and obtained from his residents and dressers a stiff level of work and was not slow to rebuke anyone thought to be idling. His manner was often abrupt, and some found it frightening, but many were drawn by the character of a teacher who quite demonstrably drove himself hard and was asking from his juniors a standard equal to his own. Though the love and admiration inspired in successive generations of dressers were not always shared by their fellows, no one would ever deny that his devotion to the hospital and medical school had made some impact on their lives. He served the institution with his whole heart, as dean, as chairman of the medical committee, as a teacher, and as a surgeon prepared to work day and night. In his retirement his observations on the concept of a statutory "session" of work were characteristically pointed. Shy, abrupt, twinkling with amusement when pleased and happy, intolerant of unsupported dogma, alert to any change if he thought it sound, "Bill" was a surgeon, a teacher, and a whole man whose life many old students will gratefully remember to-day.

H. P. H. writes: Perhaps the single most important experience in one's whole professional career is that of a first house-appointment; and in March, 1929, I had the good fortune to become house-surgeon to Gwynne Williams. His reputation among students was high. On his ward rounds they had experienced his insistent common sense. He was known not to suffer fools gladly; and fearsome, if apocryphal, stories were told of his prowess as an examiner. In short he was a treasured character in his hospital. It was therefore with some trepidation that I entered on my appointment and on what was to prove one of the most enjoyable six months of my life. Gwynne Williams was the ideal chief for a young houseman. He trusted one completely; but always appeared, apparently fortuitously, at exactly the right moment. His restraint and forbearance were as exemplary as they were unexpected; it was only afterwards that one realized the strain that one's fumblings must have put on his patience. He taught by example. He did all his own emergency operations, and generations of house-surgeons will remember the staccato conversations over the telephone in the middle of the night—"What is it?" "Right. Theatre twenty minutes"—no questioning, no doubt; you were his house-surgeon and he accepted you as a responsible partner. It is no wonder that those who had served under him gave him a special place in their affections—a feeling which he reciprocated even when, as sometimes happened, they fell by the wayside and became physicians. It is therefore with a real sense of personal loss that we heard of his death. Gwynne Williams was the type of man who has helped to build up that professional tradition which is epitomized in the public mind by the word "doctor."

M. D. SHEPPARD, M.B., F.R.C.S.

Mr. M. D. Sheppard, senior surgeon at the Chelmsford and Essex Hospital and consulting surgeon to the North-east Metropolitan Regional Hospital Board, died suddenly on February 4. He was 52.

Melvill Digby Sheppard was born in Capetown on June 5, 1905, and spent his early years in Java and Australia. Educated at Scotch College, Perth, Western Australia, he came to London to study medicine at University College Hospital in 1924. Qualifying in 1929, he graduated M.B., B.S. in the following year, and after holding house appointments at his own teaching hospital, at the Royal Surrey County Hospital, and at the Royal Salop Infirmary, where he was resident surgical officer, he took the F.R.C.S. in 1932. In the same year he went into general practice in Chelmsford as a partner of the late Dr. Henry W. Newton and the late Dr. C. W. Alford. He was immediately elected to the surgical staff of the Chelmsford and Essex Hospital and quickly made a name for himself as one of the most able surgeons in the district. In 1940 he gave up general practice to devote himself entirely to consulting surgery. Besides being on the general surgical staff of a number of hospitals in and around Chelmsford, he was consulting genito-urinary surgeon to the Ongar Hospital and surgeon in charge of the genito-urinary department at the Chelmsford and Essex Hospital. From 1946 to 1948 he was honorary secretary of the Mid-Essex Division of the B.M.A., and since then, in spite of leading a very busy life, he had helped the Division as assistant secretary.

A colleague writes: By the sudden death of Mr. M. D. Sheppard the profession has lost a first-class surgeon and his innumerable patients a wonderful and sincere friend. He was an indefatigable worker, and his energy was phenomenal. He conditioned himself to taking only a little sleep, and he gave every minute of his waking day to his work and to the care of his patients. He had a wonderful zest for living, but allowed himself little time for recreation, though he played tennis in the summer and squash in the winter with the same enthusiasm that he showed in his work. A keen and expert photographer, he applied this accomplishment to his clinical work. Although a general surgeon, his main interest was in genito-urinary work, and in this specialty he had a host of friends and admirers in this country and in many other parts of the world.

Some years ago Mr. Sheppard founded the Chelmsford and District Home and Overseas Nursing Scholarship Fund, and through his drive and enthusiasm this has flourished and enabled many nurses of the Chelmsford group of hospitals to gain postgraduate experience of nursing in this country, America, and many European countries. It has already been proposed that this fund shall be called the Melvill Sheppard Memorial Scholarship Fund for Nurses, and thus his memory and his name will live on for all time.

The medical profession has lost a great man, who by his energy and inspiration accomplished much in all too short a life. With his widow Barbara and his mother we mourn the death of a true and gallant colleague.

A. C. HALLOWES, *M.C.*, M.B., B.Ch.

Dr. A. C. Hallowes died at his home at Leek, Staffordshire, on January 20, at the age of 72.

Arthur Collis Hallowes was born in County Wicklow on December 26, 1885, a member of the Irish branch of a family whose original home had been in Derbyshire. He was educated at Dun Laoghaire, Kingstown, and later studied medicine at Trinity College, Dublin, graduating in 1910. His first appointment was as house-surgeon at Chorley Dispensary and Rawcliffe Hospital, Lancashire, and a year later he came to Leek, where he was assistant to Dr. Edgar Sommerville. When war broke out in 1914 he was commissioned in the R.A.M.C. He was awarded the Military Cross for gallantry during the first battle of Cambrai in 1917. Of the many organizations in which he was interested, the British Legion will miss him most, for as county president he was one of their most respected and popular members. Last May every British Legion branch in North Staffordshire contributed to the gold badge which he was awarded—the highest honour the Legion can bestow.

J. S. R. writes: By the death of Dr. Hallowes, Leek has lost one of its best-known citizens. A member of the British Medical Association since he qualified, he had been chairman of the North Staffordshire Division and also president of the North Staffordshire Medical Society. At the inception of the National Health Service he was appointed vice-chairman of the executive council for Staffordshire, and in 1951 he became chairman, an appointment he held until his retirement in 1956. For the 16 years before his retirement he was also medical officer of health for Leek urban district. All those who at some time or other had cause to call on Dr. Hallowes's professional services will have very vivid memories of his skill and sympathy; to many of them he was not only doctor but also friend and adviser. He was the ideal general practitioner, and his memory will live long in Leek as a true family physician who gave unstinted service in his professional life and also in the public affairs of the district. Dr. Hallowes is survived by his wife, son, and daughter, to whom we extend our sympathy in their great loss.

Sir ERNEST KENNAWAY, D.M., D.Sc., F.R.C.P. F.R.S.

The obituary of Sir Ernest Kennaway was printed in the *Journal* of January 11 (p. 104).

Dr. I. HIEGER writes: It was my great good fortune to have been Kennaway's assistant from 1924 until his retirement from the directorship of our Institute in 1946. My first meeting with him was in August, 1924, when Drummond sent me down to Fulham to see him with instructions to "make yourself indispensable." The first impression was of a gigantic figure in shirt-sleeves and braces exuding formidable power—some sort of high-speed dynamo. On closer acquaintance he had a quite youthful face: a dark moustache which he would stroke when pleased; his eyes, which were then a deep crystalline green, showed the depth of his understanding; the forehead was of alarming width and height; and he wore small blued-steel spectacles which gave him a slightly mandarin-like appearance.

What was the secret of Kennaway's magical personality? Was it his dignity, intellectual integrity, or his superb memory? Was it his world-wide range of interests, awareness of others, or his singleness of purpose? The compounding of his qualities made almost all of us his willing slaves. I was hushed, not entirely by the music of his voice but by the marvellous fitting together of the thoughts, as though the parts had been lying there all the time higgledy-piggledy, and when he spoke they became illuminated and fell into place. While our team was working on the discovery of the carcinogens Kennaway brought us through the dark tangle of the unknown like some fearless guide taking children by the hand and leading them with sure steps out of a jungle at night. After an interview I felt humbled; my mistakes had been revealed, but I had to *do* something—I had had transmitted to me a minute fragment of his inexhaustible energy. When he became interested in someone his kindness was overwhelming, but this capacity for love unfitted him for the political rat-race. He had a tempestuous nature, and his passion was the pursuit of truth: he therefore loathed shams and propaganda of any kind. As a result he did not take to the technique of the committee-room, and his adversaries made rings round him.

Dr. H. C. SQUIRES, C.M.G., writes: Ernest Kennaway was one of my oldest professional friends. We went up to Oxford the same term, two of a body of 18 medical students starting their training, of whom no fewer than seven were destined to become Fellows of the Royal College of Physicians of London. I spent my fourth year working as Kennaway's colleague in Professor Gotch's laboratory. From then our paths separated, but throughout the years we never lost touch, and it was my privilege to possess Lady Kennaway's and his friendship to the end. Others have spoken with more specialized knowledge of his scientific attainments and original work. What remains most vividly in my memory is his personal qualities. Never once did he allow physical disabilities—and these were severe—to dictate a sheltered retirement. Adapting himself with patience, skill, and ingenuity to his working capacity, he found the days too short to do all that he had in mind, and hoped that he would be given the opportunity to continue for some time longer. There was "still so much to do." And through all he was sustained by Lady Kennaway's unobtrusive help and collaboration. His companionship was exciting. His humour, at times sardonic, at times somewhat caustic, never seemed unfair or unkind. His keen analytical mind was at the service of those who sought his advice. To those of his own generation his loss is quite irreparable.

Medical Notes in Parliament

Suicide and Attempted Suicide

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Secretary of State for the Home Department on February 6 if he would introduce legislation to amend the law relating to suicide and attempted suicide.

Mr. R. A. BUTLER said that he was not satisfied that any change in the law was desirable.

Mr. ROBINSON also asked if the Home Secretary was aware of the considerable and growing opinion in the medical and legal professions, and among the general public, that the legal view of suicide was more and more at odds with society. Had not the time come to take this matter completely outside the category of criminal offences? Mr. BUTLER replied that the present concept of suicide as a crime had its roots in religious belief. Although it was true that there was greater sympathy and understanding for suicides and would-be suicides, there was no evidence in his possession that the alteration of the basic concept would be universally acceptable to public opinion. He did not underestimate the point that had been put to him; he was simply trying to assess the present position.

Car Parking in Harley Street Area

Sir WAVELL WAKEFIELD (St. Marylebone, Con.) asked the Home Secretary why steps were not being taken by the police to remove long-term car-parkers from the Harley Street, Wimpole Street, Weymouth Street, and New Cavendish Street area so that doctors might have access to their own consulting-rooms, instead of towing away doctors' cars from outside their own residences and consulting-rooms.

Mr. DAVID RENTON, Under-Secretary, Home Office, said that the relevant regulations did not empower the police to remove cars from the roads merely because they were parked for long periods or obstructed access to premises, but only where they interfered with the passage of other vehicles near a road junction, or were parked so far from the edge of the carriageway, or so near another vehicle, as unduly to restrict the space available for the passage of other vehicles. The police must be free to remove a doctor's car in such circumstances when the owner could not be traced; but only a small proportion of the cars removed in the area referred to belonged to doctors.

Sir WAVELL WAKEFIELD said there was very great difficulty in this area because of the number of cars parked which had no business or need to be there. Could not some steps be taken to make access freer to doctors and their patients in this area which had been established for medical purposes? Mr. RENTON replied that he was sure that doctors would not wish to claim the privilege of obstructing traffic. Doctors' cars were not removed if the owners could be traced: the Commissioner of Police had recommended that where doctors had to park in this area they should leave a note on the windscreen bearing their name and the address where they could be found. Sir WAVELL WAKEFIELD

said he knew that this had been done in a number of cases where doctors had left their address on a note on the windscreen, and no notice had been taken of it at all. Mr. RENTON said that if he knew of actual cases where this had happened he should let the Home Secretary have details.

Shoe-fitting Fluoroscopes

Mr. FRANK ALLAUN (Salford, East, Lab.) asked the Secretary of State for the Home Department if he would make a statement about his discussions with manufacturers and users on the dangers of shoe-fitting fluoroscopes. Mr. RENTON said that, after receiving advice last year from the Radioactive Substances Advisory Committee, the Home Secretary had put certain proposals affecting the design and use of shoe-fitting fluoroscopes to the manufacturers of these machines and to representatives of their users. He had received their comments on these proposals and was now considering them. Mr. ALLAUN then asked if the Minister felt the machines' "gimmick" value was equal to the radiation risk involved, particularly to children. Was he aware that they had recently been banned in Sweden and in a number of States in America and that legislation was now pending in France? In answer to the last question, Mr. RENTON said there was a case in Denmark, but it appeared that the trouble had been caused in an isolated instance by a faulty machine, which in any case was different from the type used in this country. Until they had considered these proposals he should not care to answer the first rather difficult supplementary question.

Control of New Drugs

Mrs. HARRIETT SLATER (Stoke-on-Trent, North, Lab. and Co-op.) asked the Secretary of State for the Home Department what precautions were taken to protect the public from the marketing of new drugs which might be likely to cause harm to the public if used without proper safeguards.

Mr. RENTON stated in reply that there were special provisions for the control of drugs coming within the scope of the Dangerous Drugs Act or the Therapeutic Substances Act. As regards other drugs, before placing new substances on the market manufacturers took every precaution, if necessary by laboratory tests and clinical trials, to ensure that they were not harmful. In appropriate cases where it was found, either before a drug had been marketed or afterwards, that it might have harmful effects, the Poisons Board were asked to consider whether it should be controlled as a poison.

Mrs. SLATER said there was growing concern at the amount of drugs being put on the open market and that could be bought freely. There had been several cases of people who had suffered badly as a result; some had landed in mental homes and some had died. It was true these drugs were referred to the Poisons Board before being put on the open market. Mr. RENTON replied that if she was referring to new drugs the matter was one for the Minister of Health. A great many well-known substances were harmless when taken in moderate quantities, and dangerous only if taken in excess. There would be no point in making such substances into "poisons." In any event it was for the Poisons Board to use its initiative in this matter. Mr. R. MELLISH (Bermondsey, Lab.) said there was one drug on the market—which he would not at that stage name—about which some authorities had already written to the Poisons Board with no success, and which had caused a number of deaths because it became dangerous once it had been taken by some people. Mrs. SLATER said she also had written to the Home Office and the Ministry of Health about the same drug. Last year the Home Secretary promised to give consideration to it, but nothing had been done.

Mr. RENTON told Mrs. SLATER that he could not yet say when the report of the Poisons Board on drugs liable to produce harmful effects if taken in excess would be ready. It was a difficult and complicated scientific question, and the Board must be given time to work out its answer.

Research on Mental Disorder

Mr. KENNETH ROBINSON asked for figures giving the total sums expended by the Medical Research Council in each of the last three years for which figures were available, and the relative amount spent on research into mental disorder. Mr. D. WALKER-SMITH informed him on February 5 that the total expenditures by the Medical Research Council, together with the corresponding figures for expenditure on research into mental health, were:

	Total Expenditure	Research into Mental Disorders
1954–5 ..	£2,177,247 ..	£23,300
1955–6 ..	£2,480,656 ..	£30,000
1956–7 ..	£2,688,779 ..	£58,000

The amounts quoted, he added, did not take account of expenditure of a similar order in the fields of neurology and psychology which were closely allied to psychiatry.

Domiciliary Psychiatry: Experiments at Worthing

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health whether he was aware that two whole-time and one part-time psychiatrists, assisted by a small number of ancillary staff, had during the first ten months of 1957 reduced the number of admissions to mental hospitals in the Worthing area by 324 cases, compared with the same period in the previous year; and if he would make an actuarial investigation into the approximate saving of hospital costs thereby brought about, bearing in mind that a figure of £560 17s. 7d. per case was the average hospital cost of each admission, being the total cost of the patient between the time of admission and time of discharge.

Mr. RICHARD THOMPSON, Parliamentary Secretary, replied on February 3 that he was aware of the results reported in the first year of this two-year experiment, which he was watching with great interest. It was not possible to estimate any financial saving which might result; although there had been fewer admissions to hospital, there was during the year no appreciable change in the number of patients resident in the hospital. The net expenditure on this experiment during the first ten months of 1957, he also stated, was £15,753. Part of the cost was met by a grant from the Nuffield Provincial Hospitals Trust.

Flying Personnel Research Committee

Mr. GEOFFREY DE FREITAS (Lincoln, Lab.) asked the Secretary of State for Air on February 7 what were the terms of reference of the Flying Personnel Research Committee and the composition and the qualifications of its members. Mr. GEORGE WARD replied: The Committee was appointed to advise the Secretary of State for Air on the medical aspects of all research affecting safety and efficiency in flying, including problems associated with the scientific selection and training of personnel, measures designed to maintain their physiological and psychological efficiency, the human problems associated with the use of guided missiles; and to advise similarly, when called upon, the Admiralty, the War Office, the Ministry of Transport and Civil Aviation, and the Ministry of Supply.

The chairman of the committee was Air Marshal Sir Harold Whittingham. The members were Sir Frederic Bartlett, F.R.S., Dr. E. A. Carmichael, Professor A. Bradford Hill, F.R.S., Professor Sir Bryan Matthews, F.R.S., Surgeon Captain C. B. Nicholson, Air Marshal P. B. Lee Potter, Group Captain H. L. Roxburgh, Sir Charles Symonds, and Air Commodore J. S. Wilson.

Licensing of Nuclear Reactors

Mr. RICHARD FORT (Clitheroe, Con.) asked the Paymaster-General what steps the Government intend to take to protect the public against risks of radioactive contamination resulting from the operation of nuclear reactors by bodies other than the Atomic Energy Authority.

In a written reply on February 10 Sir IAN HOROBIN, Parliamentary Secretary to the Ministry of Fuel and Power, announced that the Government intended to introduce legislation to ensure, by a system of licensing and inspection, that nuclear reactors on land are made effectively subject to control in the interest of public safety. All owners of such reactors would be subject to the same duty as the Atomic Energy Authority of preventing damage to property or personal injury from radioactive contamination. They would therefore be liable to pay compensation for such damage even if it was due to an unavoidable accident, except of course to the extent that the claimant injured had been guilty of contributory negligence. In order to make this provision effective a reactor owner would be required to insure his liability or to show that he was holding adequate liquid assets. In these circumstances the Government had decided that it would be right to put some limit on the amount of compensation which reactor owners might have to pay in respect of any one incident. They proposed, therefore, to include in the legislation a provision fixing this limit at £5m. in respect of each installation, a figure which they were advised was much more than adequate to cover any reasonable foreseeable risk. The insurance market had informed the Government that it was ready to provide the necessary cover. The liability of the Atomic Energy Authority would be unaffected, but problems of reactors in ships, submarines, and aircraft required further study in view of their international aspects.

Windscale Accident and London

Mr. R. MASON (Barnsley, Lab.) asked the Prime Minister to what extent the radio-iodine content in the atmosphere increased in the London area following the Windscale atomic reactor accident; by how much it had now decreased in activity; and whether he would instruct the Medical Research Council to report to what extent it may have proved harmful genetically to all who were affected by it.

Mr. BUTLER said he had been asked to reply. Radioactive iodine was detectable in the atmosphere over London after the Windscale accident on October 11, 12, and 13, but in very much smaller amounts than in the Windscale area. By October 14 the level had fallen below the limits of detection. At the Prime Minister's request, the Medical Research Council considered possible hazards to human health, including genetic hazards, arising from the accident. Its report, published as Annex III of the White Paper on the accident (*Cmd.* 302), concluded that it was

"in the highest degree unlikely that any harm was done to the health of anybody, whether a worker in the Windscale plant or a member of the general public."

Disseminated Sclerosis Vaccine

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked the Minister of Health on February 10 whether his attention had been called to the treatment of disseminated sclerosis by the Margoulis-Choubladze vaccine; and to what extent the results obtained by its use had been successful. Mr. WALKER-SMITH replied that he knew of this vaccine, but was advised that the evidence at present available was not sufficient to enable an opinion to be given on its efficacy or safety in treatment.

National Heart Hospital

Sir WAVELL WAKEFIELD asked the Minister when he expected to approve the extension of the National Heart Hospital in London, the plans for which were originally forwarded to his department in 1949. Mr. WALKER-SMITH stated that this was a large and expensive scheme which had been subject to a considerable revision since it was first submitted by the board of governors in 1950. He hoped to be able shortly to authorize the board to proceed with their latest proposals.

Domiciliary Visits

Mr. HASTINGS asked how many domiciliary visits were made by consultants and senior hospital medical officers for which claims for payment had been submitted to the four metropolitan regional hospital boards during 1956–7 in respect of general medicine, general surgery, gynaecology, anaesthetics, diseases of the chest, paediatrics, ophthalmology, orthopaedics, otorhinolaryngology, pathology, physical medicine, psychological medicine, radiology, tropical medicine, and urology, respectively.

Mr. R. THOMPSON, the Parliamentary Secretary, provided the following figures of the numbers of visits. Information about the number of these visits for which payment was not claimed, he added, was not available.

Specialty	Visits by	
	Consultants	S.H.M.O.s
General medicine	24,470	2,524
,, surgery	15,205	732
Gynaecology and obstetrics	4,538	387
Anaesthetics	169	11
Diseases of the chest	983	405
Paediatrics	3,352	214
Ophthalmology	2,506	494
Traumatic and orthopaedic surgery	4,101	289
Otorhinolaryngology	2,935	87
Pathology	3,853	1,043
Physical medicine	1,375	6
Psychiatry	5,345	787
Radiology	2,980	Nil
*Urology	Nil	,,
*Tropical medicine	,,	,,

* Some visits may have been made and classified under another heading.

Hospital Beds.—At the end of 1956 there were in England and Wales 5,942 amenity pay beds compared with 6,086 in 1952, 5,723 private pay beds (5,726), and 496,563 other beds (495,556).

Milk Consumption.—Sales of milk in the United Kingdom for liquid consumption, excluding school and welfare milk, during 1956 and 1957 were 1,292.6 million and 1,272.1 million gallons respectively.

Gas Poisoning Accidents.—During the year ended September 30, 1957, the provisional figure for deaths from accidental gas poisoning in homes and residential institutions in England and Wales was 572. This figure excludes cases of suicide.

Medico-Legal

LESS FORMALITY: EVIDENTIAL IMPLICATIONS

[FROM OUR LEGAL CORRESPONDENT]

As discussed in the January 25 issue of this *Journal* (p. 212), the Minister of Health has accepted the very strong recommendation of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency that so far as possible patients should be admitted to mental hospitals informally. His advisers agree with the view expressed by the Commission that under the law as it stands mentally defective patients can be admitted to and receive care in mental deficiency hospitals and certified institutions without the use of the procedures laid down in the Mental Deficiency Acts, 1913 to 1938; but they recognize that there would be no power of detention in relation to patients so admitted.

One of the more important incidents of unsoundness of mind is that it involves disabilities in the civil law. A person of unsound mind cannot make valid contracts, cannot make a valid will, and cannot contract a valid marriage. There are exceptions to these rules, but the principle is that to contract, to make a will, or to marry, calls in each case for an act of conscious reason. Unsoundness of mind for this purpose accordingly means a lack of the reasoning power necessary to perform the operation in question. Whether it is present or not is a matter to be proved by evidence. One way of proving unsoundness of mind is to prove an order of the Court of Protection relating to the

management of the patient's property. It is the Court of Protection which exercises at first instance the jurisdiction to look after the affairs of those who by reason of unsoundness of mind cannot look after their own. Its predecessor, the Master in Lunacy, had his name changed by the Management of Patients' Estates Rules, 1934, to the Management and Administration Department, a draftsman's masterstroke which in a world where institutions were becoming more and more known by their initials could not and did not last long.

Orders relating to the management of a patient's property can in theory still be made as a result of an inquisition, the classic example of which is to be found in *Handley Cross*. Under the Lunacy Act of 1890, however, they could also be made in the cases among others of people detained as of unsound mind or sent to or placed in institutions or certified houses or under guardianship in accordance with the Mental Deficiency Acts or received as temporary patients under the Mental Treatment Act, 1930.

Accordingly the Minister's new policy is likely to result in evidential difficulty when the question of civil capacity arises. Instead of producing as prima-facie evidence an order of the Court of Protection which would probably have been available had the patient been admitted under Mental Deficiency Act procedures, medical evidence will be necessary as to the state of mind of the informally admitted patient, whether the question is seriously in dispute or not.

DIMINISHED RESPONSIBILITY DEFENCE

[FROM OUR LEGAL CORRESPONDENT]

On January 30[1] Albert James Matheson, aged 51, was found guilty of the capital murder of Gordon Lockhart, aged 15, whose mutilated body was found in a sump under the boxing ring of the hall in Newcastle where Matheson was employed as a handyman. Matheson, who was a sexual pervert, had formed an unnatural association with the boy. He told the police that he had taken £35 in a registered envelope out of the boy's pocket and that was why he had killed him. He was charged with capital murder on the basis that it was committed in furtherance of theft.

The defence was that Matheson, although not insane in the normal sense, in that he knew right from wrong, suffered from abnormality of mind such as to diminish his responsibility for what he had done, and that he ought therefore to be convicted of manslaughter, not murder. The question was, was his mentality so abnormal, due to arrested or retarded development or disease, that he was not mentally responsible for what he had done? Dr. Ian Pickering, senior medical officer of Durham Prison, gave evidence that Matheson, who was diagnosed as a psychopathic personality in 1943, had between 1935 and 1943 been much given to self-injury, and had been a voluntary patient in a mental hospital in September, 1957. His mental age was less than that of a boy of 10, and was in Dr. Pickering's view abnormal at the time of the act to an extent which substantially interfered with his responsibility. His idea of right and wrong was very elementary. Dr. Robert Orton, consultant psychiatrist at the Royal Victoria Infirmary, Newcastle, agreed with Dr. Pickering's view, and Dr. Thomas Cuthbert, consultant psychiatrist to the Newcastle Hospitals Board, added that Matheson had no feeling of remorse or of having done wrong, and that the question of right or wrong hardly ever entered his mind.

In his summing-up, the judge, after dealing with the background of the case, directed the jury that, if they were satisfied that Matheson was suffering from abnormality of the mind which substantially impaired his mental responsibility, the only verdict open to them was manslaughter. Sexual perversion was not an abnormality of the mind, but an abnormality of morals.

After an absence of 65 minutes the jury returned a verdict of capital murder, and the judge sentenced Matheson to death.

[1] *Manchester Guardian*, January 31.

UNFITNESS TO ATTEND COURT

[FROM OUR LEGAL CORRESPONDENT]

It not infrequently happens that someone falls ill at a time when he has to appear in court as a party or a witness, and that he is not fit to do so. It is then necessary for his lawyers to apply for the case to be adjourned. In English law no one can be tried on a criminal charge without being present, and there are few civil actions which can be safely fought in the absence of the parties. If the patient is only a witness, he is usually a witness whose evidence is vital to the decision of the case. To grant an adjournment on the ground that a party or witness is ill the court will require a medical certificate, and the certificate to be effective for the purpose for which it is required must state not only that the patient is ill, but that he is unfit to attend court and why. If there is a doubt about the bona fides of the application for the adjournment the court can and occasionally does require the certifying doctor to attend for cross-examination before granting the application. Any doctor asked for such a certificate should therefore be sure he includes in it the information the court will need. Sometimes he may not be told why the certificate is wanted, and if he is not he is hardly to be blamed if the court finds fault with it.

The requirements of such certificates are illustrated by what happened when Mr. George Dawson did not appear in court at the resumed hearing of his public examination at Kingston in his bankruptcy on January 14, 1958.[1] A medical certificate was sent to the Official Receiver in these terms:

"This is to certify that Mr. Dawson is suffering from gastro-enteritis and is unfit to follow his occupation."

The Official Receiver observed that presumably Mr. Dawson had not told his doctor that he was under order of the court to attend. The Registrar commented that, as the certificate did not say that Mr. Dawson was unfit to attend court, for the purposes of the court it was absolutely useless. If there was to be any further application for adjournment on medical grounds it must be supported by an affidavit from the doctor giving the certificate, and the certificate must state that Mr. Dawson was unfit to attend.

DEATH FROM IMPACTED ASPIRIN TABLET

[FROM AN EXPERT IN FORENSIC MEDICINE]

Ronald Strowger, aged 10 months, was convalescing satisfactorily from bronchitis. On the morning of January 9, however, he was fretful and refused his midday soup. In the hope that he would rest and not be disturbed by his elder brother and sister, his mother gave him a spoonful of honey, which he took well, followed by a "junior" aspirin. He had swallowed these tablets whole before and the tablet was not crushed up on this occasion. His mother sat him on her lap and then placed him on a table to wrap him in a shawl, when she saw his face go blue and, despite efforts to make the child vomit and turning him upside down, he died in a neighbour's arms in a matter of minutes.

Post-mortem examination revealed that the aspirin tablet had lodged between and below the vocal cords, effectively blocking the airway, and the cause of death was given as asphyxia due to obstruction of the larynx by impaction of an aspirin tablet. At a subsequent inquest the coroner recorded a verdict of death from misadventure.

Comment

Asphyxial deaths in young children as the result of inhaling foreign bodies are not uncommon. Peanuts, berries, wheels of toys have all been incriminated from time to time. Accidental poisoning due to the ingestion of tablets designed for the parent again takes a small toll, sugar-coated iron

[1] *Birmingham Post*, January 15, 1958.

preparations being perhaps the most blameworthy. But death from a single tablet in therapeutic dosage must be rare.

There are many preparations of children's aspirin now on the market, most of them containing between 75 and 200 mg. of aspirin with flavouring and sweetening. Their diameter averages about 8 mm., a size which allows impaction in the larynx. However, since children's aspirins are designed to save the child tasting the bitter aspirin, there is no need for them to be swallowed whole. While the appropriate dosage for age is generally printed on the bottles, instructions as to the advisability of crushing the tablets into a vehicle such as honey or jam in the case of children under 2 years are often omitted. This advice might well be given.

Vital Statistics

Week Ending February 1

The chief variations in the trends of the notifications of infectious diseases in England and Wales during the week ending February 1 were rises of 1,135 for measles, from 2,338 to 3,473, 135 for dysentery, from 829 to 964, 76 for whooping-cough, from 569 to 645, and 59 for scarlet fever from 821 to 880. Pneumonia notifications numbered 520, a fall of 27 from the previous week's total. The 97 influenza deaths were 10 fewer than in the previous week.

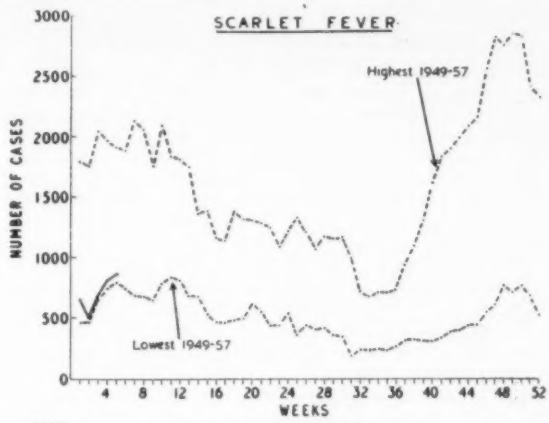
The largest rises in the incidence of measles were 100 in Leicestershire, from 132 to 232 (Leicester C.B. 177); 86 in Devonshire, from 77 to 163 (Plympton St. Mary U.D. 64); 80 in Southampton County, from 140 to 220 (Havant and Waterloo U.D. 86, Portsmouth C.B. 59); 77 in Yorkshire North Riding, from 159 to 236 (Middlesbrough C.B. 168); 68 in Somersetshire, from 69 to 137 (Taunton M.B. 44, Axbridge R.D. 37). Only small fluctuations were recorded in the local returns of scarlet fever. The largest rises in the number of notifications of whooping-cough were 26 in Kent, from 27 to 53, and 26 in Warwickshire, from 45 to 71, and the largest fall was 25 in Yorkshire West Riding, from 76 to 51. 2 cases of diphtheria were notified, being 1 more than in the preceding week.

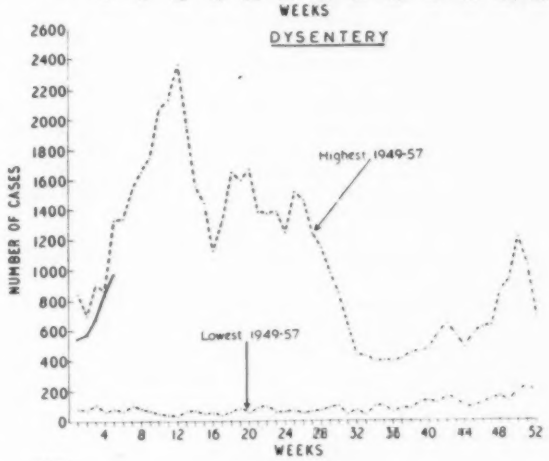
The notifications of acute poliomyelitis numbered 11 and were the smallest total for almost two years. The cases were 14 fewer for paralytic and 1 more for non-paralytic cases than in the preceding week. The only administrative area with 2 cases was Buckinghamshire, Newport Pagnell U.D.

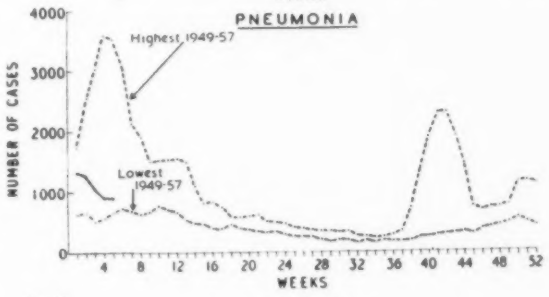
The incidence of dysentery is now over twice that at the end of December. The largest changes in the returns during the week were a fall of 117 in Lancashire, and rises of 75 in London and 45 in Yorkshire West Riding. The chief centres of infection were Lancashire 339 (Oldham C.B. 115, Middleston M.B. 39, Manchester C.B. 30, Chadderton U.D. 21, Liverpool C.B. 20, St. Helens C.B. 20, Eccles M.B. 13, Blackburn R.D. 13, Crompton U.D. 11, Salford C.B. 10), Yorkshire West Riding 144 (Barnsley C.B. 36, Sheffield C.B. 25, Leeds C.B. 15, Thorne R.D. 13, Saddleworth U.D. 11, Bradford C.B. 10, Huddersfield C.B. 10), London 137 (Finsbury 39, Bethnal Green 18, Islington 18, Fulham 13, Hackney 12, Lewisham 11), Durham 55 (Sunderland C.B. 11), Yorkshire North Riding 47 (Middlesbrough C.B. 35), Middlesex 27 (Ealing M.B. 12), Cambridge 24 (Cambridge M.B. 12), Chesterton R.D. 12), Warwickshire 22 (Birmingham C.B. 16).

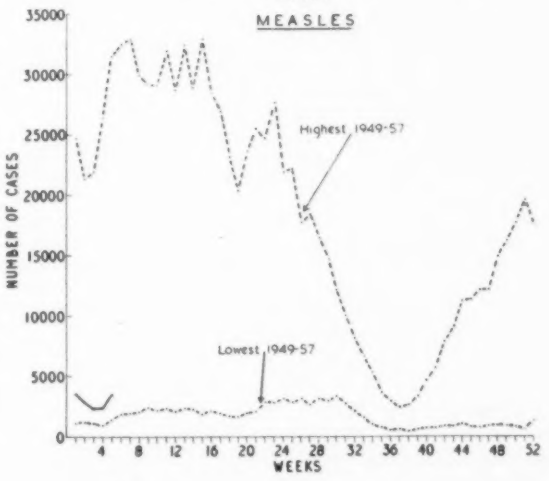
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - -, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Acute Respiratory Disease in Babies

Since January 20 the number of babies needing admission to hospital in London has risen, and between a third and a half of all admissions arranged by the Emergency Bed Service for cases of acute respiratory disease have been of children aged under 5. Most of these children have been aged 3 months to 2 years. No corresponding increase in the need for hospital beds by older patients has been noted. There are indications of a similar situation in Birmingham.

The babies usually have a history of a cold for two or more days. Their condition then deteriorates, often rapidly, with evidence of disease in the lower respiratory tract. The more severely ill children have been restless and cyanosed; some have shown intercostal recession on inspiration and other evidence of obstructions of the respiratory tract, but signs of consolidation have not been prominent. A few deaths have been recorded. In many cases oxygen therapy has been essential, whereas antibiotics do not seem to have greatly affected the course of the illness, though they may have helped to avert secondary infection. No evidence has been obtained suggesting a bacterial cause.

In November, 1953, outbreaks resembling the present one were observed in London, Liverpool, and Manchester,[1] and another outbreak in Sunderland in 1953, fully described by J. B. Heycock and T. C. Noble,[2] seems very similar. These authors refer to the prevalence of such illness in other years. Efforts to show that the illness was due to influenza or other viruses were unsuccessful and the problem of aetiology is still unsolved.

Additional information may be obtained if outbreaks are reported to medical officers of health as soon as they are recognized.

Marriages and Divorces in 1956

In England and Wales in 1956 there were 352,944 marriages, giving a rate of 15.8 persons marrying per thousand population.[3] This was lower than in 1955 but higher than in 1953 and 1954. The Eastern region had the lowest marriage rate with 13.4, and London and South-eastern the highest with 17.0 persons marrying per thousand population. 120 of the men and 2,681 of the women were aged under 17 at marriage, and 5 men, though no women, were aged 90 or over at marriage; the 5 men were all widowers; 2 of them married spinsters and 3 widows. The commonest age for men to get married was 23 and for women 21. By contrast with 50 years ago, relatively more people marry at younger and also older ages, and the proportion of marriages in the middle years of life is lower. The explanation of this is that, in addition to the present tendency for people to marry younger than they used to do, thus reducing the numbers of marriages among middle-aged people, widows and widowers are nowadays much more likely to marry again than 50 years ago.

Marriages dissolved by divorce in 1956 numbered 25,718 and by annulment 547. These figures are respectively about six times and three times the comparable figures of the 1930's. The figure for divorces was the lowest since the end of the second world war. The commonest age for divorce to take place is 30–34 for both husbands and wives, and 10–14 years is the commonest duration of those marriages which end in divorce. The existence of children tends to prevent divorce: in those marriages which ended in divorce, the largest number (8,934) had no children, and the next largest number (8,212) had only one child. In 188 cases of divorce there were 7 or more children of the marriage.

[1] *Report of the Ministry of Health for the Year Ended December 31, 1953*, Part 2, p. 45. H.M.S.O., 1954.
[2] Heycock, J. B., and Noble, T. C., *Brit. med. J.*, 1956, **1**, 438.
[3] *Registrar-General's Statistical Review of England and Wales for the Year 1956*, Part 2, Tables, Civil, 1958. H.M.S.O., 7s. 6d.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 25** (No. 4) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0		1	0	5	0	1
Dysentery	829	62	133	10	1	635	43	255	0	1
Encephalitis, acute	2	0		0		5	0		0	
Enteric fever:										
Typhoid	2	0	0	0		1	0	0	0	
Paratyphoid	1	0	0	0		2	0	1 (B)	0	
Food-poisoning	127	17	9	0		165	20	46	5	
Infective enteritis or diarrhoea under 2 years				13	12				14	16
Measles *	2,338	39	67	34	2	9,527	682	431	428	201
Meningococcal infection	39	6	13	1	1	23	2	17	0	1
Ophthalmia neonatorum	25	0	6	0		27	0	1	0	
Pneumonia †	917	68	380	15	7	572	35	338	21	
Poliomyelitis, acute:										
Paralytic	18	2	1	0	2	21	2	2	0	11
Non-paralytic	6	1				6	0			
Puerperal fever §	204	32	12	4		241	28	9	1	1
Scarlet fever	821	53	63	10	14	829	47	98	36	20
Tuberculosis:										
Respiratory	541	66	97	10		636	70	116	26	
Non-respiratory	58	4	14	6		30	4	9	2	
Whooping-cough	569	36	33	3	16	3,233	154	506	14	65

DEATHS in Great Towns	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	1
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	0	1	1	8	1	0	1	2
Influenza	107	15	1	0	1	12	0	3	1	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia	581	98	34	15	15	282	46	32	17	13
Poliomyelitis, acute	1	0		0	0	2	2			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	77	10	9	2	4	52	3	6	2	1
Non-respiratory		3	0	0	1		0	2	0	1
Whooping-cough	0	0	0	0	0	0	0	1	0	0
Deaths 0–1 year	261	35	32	10	18	220	21	32	7	26
Deaths (excluding stillbirths)	7,702	1107	724	132	201	5,944	784	712	156	190
LIVE BIRTHS	7,688	1139	1009	223	341	7,982	1125	1000	222	331
STILLBIRTHS	197	24	37			199	18	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Honorary F.R.C.S.—The council of the Royal College of Surgeons of England announces that the honorary fellowship of the College has been conferred on the following distinguished surgeons: Professor WARREN H. COLE, professor of surgery in the University of Illinois; Professor CLARENCE CRAFOORD, professor of thoracic surgery in the University of Stockholm; Professor F. L.-P. de G. d'ALLAINES, clinical professor of surgery in the University of Paris and chief of the American Hospital and the Hôpital Broussais in Paris; Professor C. F. W. ILLINGWORTH, Regius professor of surgery in the University of Glasgow and surgeon-in-charge of the Western Infirmary, Glasgow; Dr. CHARLES W. MAYO, a member of the staff of the Mayo Clinic and professor of surgery at the Mayo Foundation, Minnesota; and Professor HERBERT OLIVECRONA, professor of neurosurgery at the Royal Caroline Medico-Surgical Institute, Stockholm.

Bodies for Dissection.—The table below gives details of the minimum requirements, and supplies in 1955–6 and 1956–7, of bodies for dissection in Britain. Medical schools seriously short of bodies are those at Cambridge, Newcastle, and Glasgow. For the last two years the supply of bodies in London has exceeded the 10-year average (1946–56) of 220, while in the provinces and Scotland it has been below the 10-year averages of 328 and 112 respectively. Last year (1956–7) bequested bodies comprised 70% of the London supply, 44% of the provincial supply, but only 15% of the Scottish supply. Anyone wishing to arrange for the bequest of a body for dissection may obtain full details of the procedure from H.M. Inspector of Anatomy, Anatomy Office, Ministry of Health, Savile Row, London, W.1.

University Area		Minimum Requirement	Supplied 1955–6		Supplied 1956–7	
			Total	(Bequests)	Total	(Bequests)
London	.. ..	231	244	(136)	270	(174)
Provinces and Wales	Birmingham ..	26	65	(16)	53	(22)
	Bristol ..	18	48	(18)	44	(23)
	Cambridge ..	**54**	40	(9)	**38**	(11)
	Cardiff ..	13	17	(6)	11	(7)
	Leeds	23	21	(9)	27	(10)
	Liverpool ..	32	25	(5)	34	(16)
	Manchester ..	28	36	(13)	37	(16)
	Newcastle ..	**31**	14	(6)	**20**	(7)
	Oxford ..	18	32	(15)	21	(6)
	Sheffield ..	17	17	(9)	19	(15)
	Total ..	*260*	*315*	*(106)*	*304*	*(133)*
Scotland	**Glasgow** ..	**45**	28	(6)	**27**	(6)
	Edinburgh ..	49	30	(3)	45	(9)
	Aberdeen ..	18	13	(0)	15	(0)
	St. Andrews ..	10	10	(0)	10	(0)
	Dundee ..	9	12	(3)	10	(1)
	Total ..	*131*	*93*	*(12)*	*107*	*(16)*
Total for Great Britain ..		622	652	(254)	671	(323)

Clean Air Act.—By an Order (S.I. No. 167) published on February 6 the MINISTER OF HOUSING AND LOCAL GOVERNMENT has named June 1 as the second "appointed day" for the Clean Air Act, 1956. On that day all the remaining provisions of the Act will come into force. The main practical effect of the Order will be that from June 1 it will be an offence, subject to fines of up to £100, to emit dark smoke from chimneys. The ban will apply to factories, shops and offices, the funnels of ships and railway engines, and chimneys of houses, though these last rarely produce dark smoke. The Act allows certain defences in the event of proceedings—for example, if it can be proved that the dark smoke was solely due to lighting up a furnace from cold or to mechanical failure.

Liberal Medical Committee.—The Liberal Party has set up a medical and public health committee, under the chairmanship of Colonel G. F. TAYLOR, I.M.S., retired, formerly principal of the King Edward Medical College, Lahore. The committee is to advise the Liberal Party on such matters as radiation, smog, air pollution, water pollution, and all matters affecting public health and the practice of medicine. The other members of the committee are Lord AMULREE, Dr. ARNOLD BENDER, Ph.D., Professor ALEXANDER HADDOW, and Lord STAMP. Communications should be addressed to the committee's joint secretaries (Mrs. Geoffrey Taylor and Mr. B. V. Watkin) at 58, Victoria Street, London, S.W.1.

M.R.C.P.Ed.—At a quarterly meeting of the Royal College of Physicians of Edinburgh on February 4 the following were elected members:

M. M. El-Nahas, W. Horovitz, S. N. Basu, S. Nadarajah, G. Kuppuswamy, R. N. Dutta, F. E. Abdel-Gadir, C. P. Lowther, J. N. Wattie, A. M. I. Wasfi, W. J. Gomes, G. R. Sparrow, M. W. Partington, I. Hyde, H. Coll, M. N. Khan, R. A. Papworth, R. Pararajasegaram, J. F. Moodie, N. J. W. Royston, S. C. Hu, A. L. Hilton, S. P. Ram, G. B. Jain, K. Gupta, B. W. Cromie, B. K. Ahuja, and R. A. Harkness.

Type Cultures.—The catalogue of micro-organisms maintained at the National Collection of Type Cultures has been revised and issued as *Medical Research Council Memorandum* No. 35 (H.M.S.O., price 2s. 6d. net). The National Collection, which contains organisms of interest mainly to medical and veterinary workers, is maintained by the Medical Research Council at the Central Public Health Laboratory, Colindale Avenue, London, N.W.9. The M.R.C. memorandum gives details of the conditions of supply of dried cultures, the catalogue of available species (with a separate list of individual strains for special tests), and the names and addresses of other specialized collections of micro-organisms in Britain.

British Council Courses.—Among the courses this year for overseas specialists arranged by the British Council in conjunction with other organizations are three medical ones, all in London: "Anaesthesia," February 23–March 7, fee £40; "Industrial Diseases," April 13–26, fee £45; and "Rehabilitation of the Unfit," November 2–15, fee £45. The fee for each course includes the cost of board and lodging and excursions during the course. Further information may be obtained from the local representative of the British Council, if abroad; or, for those in the United Kingdom, from the director of the courses department, British Council, 65, Davies Street, London, W.1.

Merseyside Medical Art Society.—The Merseyside Medical Art Society was founded during 1957. The president is Professor B. G. MAEGRAITH, School of Tropical Medicine, Liverpool. Membership of the society is open to any medically qualified person resident on or near Merseyside. It is intended to hold an inaugural dinner in Liverpool on April 2, which will be followed by an exhibition of works of art in any medium by members of the society. This exhibition will be open to the general public. Those interested should apply to the secretary of the society, Dr. D. B. MOSSMAN, Warrington General Hospital, Warrington, Lancashire, for further information.

Sputum Disposal.—The Joint Tuberculosis Council has printed as a pamphlet its public health committee's report on "Collection and Sterilization of Tuberculous Sputum in Hospital and at Home." Copies may be obtained, free of charge, from the council's hon. secretary, Dr. R. L. MIDGLEY, Hawkmoor Chest Hospital, Bovey Tracey, Devon.

London University.—Dr. MARY BARBER has been appointed to the University readership in clinical bacteriology tenable at the Postgraduate Medical School of London.

COMING EVENTS

Institute of Dermatology.—Semi-permanent exhibition on "Drug Eruptions" until February 28.

Members' Lecture and Party.—Dr. CHARLES NEWMAN will give an "unofficial FitzPatrick lecture" at the Royal College of Physicians of London on February 28 to a meeting restricted to members of the College and their

wives. Immediately afterwards there will be a sherry party, for which tickets (10s. each) may be obtained from the secretary of the College. The last date for applications for tickets is February 17.

Fourth James Yearsley Lecture.—Mr. FRANCIS MCGUCKIN will lecture at 5.15 p.m. on March 7 at the Royal Society of Medicine on "Recent Developments in Tympanoplastic Surgery."

Child and Family Psychiatry.—A refresher course at the Ipswich and East Suffolk Hospital, March 24–28. Details from the Department of Child and Family Psychiatry, 11, Fore Street, Ipswich, Suffolk.

Society of Chemical Industry.—Conference on fundamental aspects of the dehydration of foodstuffs, March 25–27, in Aberdeen. Details from the society, 14, Belgrave Square, London, S.W.1.

British Council for Rehabilitation.—Three-day course and conference (in conjunction with the University of Aberdeen) on "Rehabilitation: Its Industrial and Social Implications," March 25–27, in Aberdeen. Details from the council, Tavistock House South, Tavistock Square, London, W.C.1.

Radiation Hazards.—Symposium on "Noxious Effects of Low Level Radiation," arranged by the Swiss Academy of Medical Sciences, March 27–29, in Lausanne. Details from the academy's secretariat, 13, Petersplatz, Basle, Switzerland.

Institute of Biology.—Second international symposium on freezing and drying, April 1 and 2, at the Beveridge Hall, Senate House, London, W.C.1. Details from the institute, 41, Queen's Gate, London, S.W.7.

Eighth Middle East Medical Assembly.—At the American University of Beirut, Lebanon, March 9–11. Details from Dr. HRANT T. CHAGLASSIAN at the university.

Prevention of Occupational Accidents.—Second World Congress, May 19–24, in Brussels. Details from the congress secretariat, 29, Avenue André Drouart, Brussels (Auderghem).

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 17

GUY'S HOSPITAL.—5 p.m., Endocrine Demonstration. Biochemical Tests of Endocrine Function. Guest speakers, Dr. W. H. H. Merivale and Dr. I. F. Sommerville.

HUNTERIAN SOCIETY.—At Mansion House, 8.30 p.m., Hunterian Society Oration by Dr. Macdonald Critchley: Animal Communication.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Mr. Murray A. Falconer: Temporal Lobe Epilepsy.

Tuesday, February 18

B.B.C. TELEVISION.—9.30 p.m., "Your Life in Their Hands," No. 2—Ray of Hope, from The Christie Hospital and Holt Radium Institute, Manchester.

BEDFORD COLLEGE.—5.15 p.m., public lecture by Dr. W. Grey Walter, Sc.D.: The Human Brain—The Physiology of Mentality (illustrated).

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. L. P. R. Fourman: Potassium Depletion.

HEATHERWOOD ORTHOPAEDIC HOSPITAL.—8.30 p.m., Mr. W. E. Tucker: Athletic Injuries (with film).

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Mr. A. T. Gray: Ointment Bases.

ST. ANDREWS UNIVERSITY.—At Physiology Lecture Theatre, 5 p.m., Dr. R. P. Cook: Investigation of the Lipids.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Dr. J. M. Holmes: Breech Presentation and Delivery.

UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., Dr. J. D. Robertson: The Cell Membrane: What Is It?

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. T. Rowland Hill: neurological demonstration.

Wednesday, February 19

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. J. L. Clegg and Dr. R. J. Stanley: Report of the Royal Commission on the Law Relating to Mental Health.

EUGENICS SOCIETY.—At Manson House, 26, Portland Place, W., 5 p.m., Galton Lecture by Professor Aubrey Lewis: Fertility and Mental Disorder.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Basal Cell Epitheliomata.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. E. H. Hudson: Use of Cortisone in Pulmonary Tuberculosis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. S. B. Osborn: Radiotherapy in Urology.

MIDLAND MEDICAL SOCIETY.—At Queen Elizabeth Hospital, Birmingham, 8.15 p.m., clinical meeting.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. Rosemary Biggs: Blood Coagulation Factors in Theory and Practice.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Star and Garter Hotel, Putney Bridge, W., 7.30 for 8 p.m., Dr. R. D. Teare: Role of the Pathologist in the Investigation of Crime.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At Leeds General Infirmary, 8 p.m., symposium: Dr. R. F. Woolmer: Measurement in Anaesthesia; Mr. D. Hill: Some Engineering Aspects of Anaesthetic Research; Dr. J. F. Nunn: Carbon Dioxide Retention During Anaesthesia.

Thursday, February 20

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Dr. G. M. Ardran and Dr. F. H. Kemp: Radiological Investigation of Infant Feeding.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor P. L. Krohn: Processes of Ageing in the Reproductive System.

HILL END HOSPITAL MEDICAL SOCIETY.—8.45 p.m., Sir W. Paul Mallinson: Psychiatric Aspects of the Health Service.

HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., discussion: Epilepsy. To be opened by Dr. Denis Williams, Dr. D. F. O'Neill, and Dr. R. E. Kelly.

LIVERPOOL MEDICAL INSTITUTION.—At Clatterbridge General Hospital, Bebington, 2.30 p.m., afternoon clinical demonstration.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.30 p.m., Mr. A. Dickson Wright: Painful Arm. Also short silent film.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Staff House, Manchester University, 8 p.m., Dr. H. J. Brennan: Terminal Apnoea.

NORTH-EAST LONDON CLINICAL SOCIETY.—At Prince of Wales's General Hospital, Tottenham, N., 2.30 p.m., meeting.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., Professor B. S. Platt: Malnutrition and Pathogenesis of Zymotic Diseases.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. M. A. Partridge: postgraduate demonstration in psychiatry.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. F. H. C. Crick: Nucleic Acids—(2) Function.

Friday, February 21

BRITISH INSTITUTE OF RADIOLOGY.—3 p.m., meeting of medical members. 5.30 p.m., short papers: Recent British Gamma-ray Beam Units. Speakers, T. Ashton, B.Sc., G. S. Innes, B.Sc., A.Inst.P., R. G. Wood, M.Sc., F.Inst.P., Dr. J. R. Clarkson, Ph.D., and J. C. Jones, B.A., A.Inst.P.

FACULTY OF RADIOLOGISTS: RADIODIAGNOSIS SECTION MEETING.—At Royal College of Surgeons of England, 4.45 p.m., Dr. G. Ansell: Radiological Findings in Patients Treated with Cortisone and A.C.T.H.

● INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. M. B. MacKenna: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. H. Scadding: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—(1) 3.30 p.m., clinical discussion for general practitioners by Mr. Wallace Black: Chronic Ulcers in the Mouth and Pharynx. (2) 5.30 p.m., Dr. T. V. L. Crichlow: Radiology of the Temporal Bone.

KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL.—4.30 p.m., 6th Dorothy Platt Memorial Lecture by Professor R. McWhirter: Recent Advances in Breast Cancer.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. I. H. Griffiths: Incontinence of Urine. (2) 4 p.m., Dr. A. G. MacGregor: Idiopathic Haemochromatosis.

ROYAL INSTITUTION.—9 p.m., Professor Alexander Haddow: Cancer Research: Its History and Prospects.

ROYAL MEDICAL SOCIETY, EDINBURGH.—8 p.m., Professor E. J. Wayne: Diagnosis and Treatment of Thyrotoxicosis.

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Faculty of Physicians and Surgeons of Glasgow, 8.30 p.m., Professor John Bruce: Surgery of the Cardio-oesophageal Junction.

Saturday, February 22

ASSOCIATION OF CLINICAL BIOCHEMISTS: SOUTHERN REGION.—At King's College Hospital Medical School, 2 p.m., scientific papers and demonstrations.

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.—At Bradford, 2 p.m., meeting.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Griffiths.—On January 31, 1958, to Barbara, wife of Dr. Glyn Griffiths, of 179, East Dulwich Grove, London, S.E., a brother for Mary Anne and Caroline—Charles William.

Jones.—On January 26, 1958, at St. David's Hospital, Bangor, to Mary (formerly Snelling), wife of Dr. Ellis Jones, a son—David Maurice.

DEATHS

Adams.—On January 27, 1958, at The Warren House, Wotton-under-Edge, Glos, George Basil Doyne Adams, M.D., D.P.H., aged 80.

Ashwin.—On January 28, 1958, at his home, Waldyve House, Market Weighton, Yorks, Richard Hamilton Ashwin, M.D., aged 83.

Brown.—On January 31, 1958, in hospital, Edinburgh, William Brown, O.B.E., M.B., F.R.C.P.Ed., of Edenside, Kelso, Roxburghshire.

Cuningham.—On January 25, 1958, Ronald William Cuningham, M.B., B.Ch., of 27, Clarendon Street, Londonderry.

Escombe.—On January 29, 1958, at 5, Eleanor Street, Grimsby, Lincs, William Escombe, M.R.C.S., L.R.C.P., aged 88.

Hignett.—On January 29, 1958, at Hove, Sussex, Lionel Watson Hignett, M.B., C.M., D.P.H., of Sheen Cottage, Loxwood, Sussex, aged 92.

Hogg.—On January 25, 1958, at 17, Boyne Park, Tunbridge Wells, Kent, Alfred Hogg, M.D., aged 89.

Howard.—On February 1, 1958, at his home, 23, Chanel Street, Hyde, Cheshire, James Howard, M.R.C.S., L.R.C.P., D.P.H., aged 80.

Maclaine.—On January 22, 1958, at his home, House of Pittyvaich, Dufftown, Banffshire, Stanley Lister George Donald Maclaine, L.R.C.P.&S.Ed., L.R.F.P.S., late of Nigeria, aged 83.

Marron.—On January 20, 1958, at 18, Christ Church Road, Doncaster, Yorks, Thomas Marron, M.B., B.Ch.

Matson.—On February 1, 1958, Neill David Matson, F.R.C.S.Ed., D.L.O., of Ynysllynlladd, Cadoxton, Neath, Glam.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Chloroquin in Rheumatoid Arthritis

Q.—*Is chloroquin of value in rheumatoid arthritis? If so, what is believed to be its mode of action?*

A.—It has been reported from a number of centres throughout the world that chloroquin is of value in the treatment of rheumatoid arthritis. Originally this substance was tried because it was found to be helpful in cases of chronic discoid lupus, and it was thought that it might benefit cases with more widely disseminated collagen abnormality. No strictly controlled trials have yet been reported, but a number of papers claiming good results were read at a recent congress of the International League against Rheumatism held in Toronto.

Prophylactic Chemotherapy after Acute Nephritis

Q.—*What are the indications for prophylactic chemotherapy after an attack of acute nephritis? If advised, how should it be given?*

A.—If the nephritis is associated with haemolytic streptococcal infection, as evidenced by a high antistreptolysin O titre, it is more likely to be acute glomerulonephritis than the rarer possibility of pyelonephritis, systemic lupus erythematosus, Henoch's purpura, or polyarteritis nodosa. Recurrences are less common than in rheumatic fever, but can be prevented in the same way. This was suggested originally by Longrope in 1942, using sulphonamide. Rammelkamp[1] has recently shown that penicillin prophylaxis more than halves the nephritis attack rate during epidemics of nephritogenic streptococcal infection.

Prophylaxis should consist of penicillin 200,000 units twice daily by mouth and should be continued at least until the child has left school. Protection should be started at any time and particularly if the child is in a crowded environment where β-haemolytic streptococcal infection may become common. No part of the world is immune from group A β-haemolytic streptococci, but isolated communities leading an open-air life probably have little opportunity for cross-infection.

REFERENCE

[1] Rammelkamp, C. H., *Ann. intern. Med.*, 1955, **43**, 511.

Pulmonary Haemosiderosis in Mitral Stenosis

Q.—*What proportion of cases of mitral stenosis develop pulmonary haemosiderosis? What type of case is specially liable to this complication, and how does it affect prognosis?*

A.—Pulmonary haemosiderosis detectable by the pathologist is common in severe mitral stenosis, but radiologically evident haemosiderosis occurs in only 10 to 20% of such cases. Radiological recognition depends on the number and distribution of the foci of haemosiderosis, the nodular lung shadow being formed by coalescence of several foci, each of which would be invisible individually. The condition occurs when the left atrial pressure is considerably elevated, causing pulmonary venous hypertension: the pulmonary arterial pressure and arteriolar resistance are not necessarily greatly increased.

A raised left atrial pressure is not the only factor concerned in producing haemosiderosis sufficient to be diagnosed radiologically, for many patients with considerable left atrial hypertension do not show it. A rapid increase in pulmonary venous pressure may be implicated, but there is no proof of this. Haemoptysis is a common accompaniment of haemosiderosis, and may be repeated and severe. The ultimate prognosis is that of the underlying mitral valve disease, but quite severe anaemia may result from repeated haemoptysis and may cause anxiety. In general, the presence of radiologically detectable haemosiderosis indicates severe disease of the mitral valve.

Work at High Altitudes

Q.—*Is it possible for a man to live and work for long periods at a height of 15,000 ft. (4.6 km.)? The work in question would be manning medium-sized earth-moving equipment.*

A.—The answer is yes. There are many places in the world, more particularly in the Andes and Himalayas, where people live and work permanently at altitudes between 13,000 and 15,000 ft. (3.9 and 4.6 km.). The highest known permanently occupied settlement is a mining camp on Aucanquileha, in Peru, situated at 17,500 ft. (5.3 km.), which was visited by the International Physiological Expedition to the Andes of 1935. The questioner is referred to Professor D. B. Dill's book *Heat, Life and Altitude*,[1] which describes the remarkable degree of acclimatization shown by the miners living there.

REFERENCE

[1] Dill, D. B., *Heat, Life, and Altitude*, 1938. Harvard University Press, Cambridge, Mass.

Sonne Dysentery Carriers

Q.—*What is the usual duration of the carrier state after an attack of Sonne dysentery? Two brothers, aged 8 and 10 years, have been passing Shigella sonnei in the stools for eighteen months. They have had a prolonged spell in an isolation hospital, and from time to time have been treated intensively with sulphonamides and various antibiotics, including chloramphenicol, streptomycin, and polymyxin. The addition of yoghurt to the diet has also been tried, but all measures have failed to alter the carrier state. What is the prognosis of this condition, and what further treatment is suggested?*

A.—It is most unusual for this carrier state to persist for so long: the great majority of patients finally lose their bacilli within a period varying from a few weeks to at most a few months. Is the identity of the organism still found in these patients established beyond doubt?

Treatment could have failed owing to inadequate dosage or insufficient duration, or because reinfection has occurred from family contacts: the terms of the question do not make it clear whether any of these factors could have operated. The most useful drugs for this purpose are the antibiotics with a bactericidal action on Gram-negative bacilli, of which there are three. These, with the usual total daily oral dose (which should be divided into three spaced individual doses), are polymyxin B, 20 mg. per kg. body weight, neomycin 50 mg./kg., and streptomycin up to 100 mg./kg. Treatment should be continued for 10 days. A combination of two of these drugs might be tried. Treatment should be in hospital, not because it involves any risk, but to ensure regular administration. Since streptomycin has already been used, and bacterial resistance to it is easily acquired, the strain of dysentery bacillus from each boy should be tested for sensitivity to it before it is given again. It would be useful to verify sensitivity to the other two antibiotics, but resistance to either of these is rare.

Hard Water and the Skin

Q.—*Why does hard water roughen the skin?*

A.—Several factors may operate in causing roughening of skin exposed to hard water. The hardness of water is commonly due to dissolved carbonates of calcium and to magnesium sulphate. Calcium carbonates combine with

fatty acids in soap to form insoluble calcium stearate, which is the major constituent of the scum formed under these conditions. Calcium stearate is not only insoluble but has a very high adhesive power for skin; indeed, it is sometimes used as a component of barrier creams. It is deposited and tends to remain on the skin.

In addition to forming calcium stearate from soap, similar compounds may be formed by the combination of calcium with the fatty acids of the sebum, and these will be deposited in intimate contact with the keratin layer and the orifice of the hair follicles. The film of calcium stearate is responsible for the rough feeling of the skin. The calcium stearate can be removed by further application of soap and water, but this in turn involves excessive defatting of the skin and consequently the roughness remains. It is also possible that in hard-water areas more alkaline soaps may be currently used in order to combat the hardness of the water and make lathering easier.

Prevention of Short-sightedness

Q.—*Is there any preventive treatment, by exercise or otherwise, for short-sightedness?*

A.—It is generally agreed that there is no preventive or curative treatment for true short-sightedness (axial myopia), in which the most important aetiological factor is heredity. Another factor, however, must be considered in certain cases—that is, nutritional. It is a well-known clinical fact that axial myopia may progress considerably during the stage of rapid growth, and it has been shown that there may be some relationship between the rate of progress of myopia and protein consumption.[1] Attention to diet and a regime which ensures a high standard of physical fitness may therefore be of importance in some cases.

REFERENCE

1 Gardiner, P. A., *Trans. ophthal. Soc. U.K.*, 1956, **74**, 171.

Sensitization to Gamma Globulin

Q.—*Does the administration of gamma globulin ever lead to sensitization phenomena, and, if so, what are their nature and frequency?*

A.—So far as is known, hypersensitivity to injected gamma globulin does not occur. Intravenous injections of gamma globulin may cause a fall in blood pressure, presumably owing to the presence of some pharmacologically active substance, and for this reason injections of gamma globulin should not be given by the intravenous route.

Horse Sera

Q.—*Caution is advised in giving anti-tetanus serum to patients who have previously received injections containing horse serum. What other preparations are made from this source?*

A.—In addition to tetanus antitoxin, horse antisera include (1) diphtheria, haemolytic streptococcus, staphylococcus, dysentery (Shiga), botulinum, and gas-gangrene antitoxins; and (2) leptospira, anthrax, pneumococcus, and meningococcus antibacterial sera. Most of the sera in the latter group have been rendered obsolete by effective chemotherapy. Diphtheria prophylactic, toxoid-antitoxin floccules (T.A.F.), also contains a small amount of horse serum, to which a person might become sensitized.

NOTES AND COMMENTS

Inoculation Campaigns and Viral Hepatitis.—Dr. F. D. F. STEEDE (Peterborough) writes: With some diffidence I write to comment on the answer given in "Any Questions?" (*Journal*, January 4, p. 55) with regard to the question of the transmission of infection in an immunization session. I feel that what is required is not a method which lessens the risk, but the simplest practical method which can be relied upon to eliminate the risk entirely. In this connexion a paper was published in the *Journal*[1] some years ago which proved that changing needles was insufficient, as in the act of withdrawal tissue fluid could be drawn up the needle to contaminate the syringe nozzle. I understood that this paper also proved that such contamination could be adequately dealt with by immersing the syringe, with the used needle *in situ*, as far as the nozzle in water at 100° C. for 10 seconds. I have used this method myself subsequently when time did not allow a fresh syringe and needle to be boiled up for each injection. I feel sure that further discussion of this subject would be of considerable general interest at the present time.

REFERENCE

1 Fleming, A., and Ogilvie, A. C., *Brit. med. J.*, 1951, **1**, 543.

Hydrogen Peroxide and Cancer Therapy.—Dr. R. A. HOLMAN (Cardiff) writes: I would like to make one or two points following the note on this subject ("Any Questions?" January 4, p. 56). With regard to my experiments using oral H_2O_2 as a carcinolytic agent in rats[1] adequate controls were maintained throughout. In all the 40 control animals the tumours progressively increased in size to some 80 mm. maximum diameter, and the animals either died or were killed to prevent further suffering. The mechanism of the action of H_2O_2 on malignant cells has been fully discussed.[2,3] On the question of the toxicity of intravenous H_2O_2 it is only fair to point out that Motawei[4] used amounts considerably in excess of 20 ml. once or twice daily. I quote from his paper: ". . . in fact 250 ml. diluted H_2O_2 were injected intravenously by the drip method without any ill effect and with marked improvement after the first injection. With 20 ml. daily injection the improvement appeared after the first week." In a later paper[5] he quotes the actual concentrations of H_2O_2 used—i.e., 250 ml. diluted H_2O_2 equivalent to 250 ml. O_2. He further emphasizes the fact well known to all workers with H_2O_2 that the commercial product contains a stabilizer and this may be toxic according to the one used. His initial experiments using H_2O_2 intravenously in dogs produced no ill effects.

OUR EXPERT replies: It is difficult to understand why the control series mentioned by Dr. Holman were not referred to in his original communication.[1] Green and Westrop[6] have recently repeated this experiment using 10 rats implanted with the Walker carcinoma, also 6 rats implanted with the Sheffield Rd/3 sarcoma. An equal number of rats were observed as controls in each group. They concluded that the treatment was completely ineffective. Neither of Motawei's papers[4,5] gave any details of the patients treated. His claim that intravenous injections of hydrogen peroxide in the amounts stated were given without ill effect does not appear to be universally confirmed by research workers in this country, who are also well aware that the commercial product usually contains a stabilizer.[7]

REFERENCES

1 Holman, R. A., *Nature (Lond.)*, 1957, **179**, 1033.
2 —— Proceedings of International Symposium of Medicine, Trieste, 1957, in press.
3 —— *Brit. med. J.*, 1957, **2**, 881.
4 Motawei, A. M., *A Preliminary Report on a New Chemotherapeutic Agent Effective in the Treatment of Malignancy and Tuberculosis*, 1954, Memphis Press, Cairo.
5 —— *Hydrogen Peroxide in the Treatment of Tuberculosis*, 1954, Memphis Press, Cairo.
6 Green, H. N., and Westrop, J. W., *Nature (Lond.)*, 1958, **181**, 128.
7 Scott, O. C. A., personal communication.

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